A STUDY ON ROLE OF URINE TRYPSINOGEN – 2 IN DIAGNOSING ACUTE PANCREATITIS

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CHENNAI

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CERTIFICATE

This is to certify that the dissertation titled ***"A STUDY ON ROLE OF URINE TRYPSINOGEN – 2 IN DIAGNOSING ACUTE PANCREATITIS"*** is the bonafide work done by ***Dr. N.SANGARA NARAYANAN,*** Post Graduate student (2011 – 2014) in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under my direct guidance and supervision, in partial fulfillment of the regulations of The Tamil Nadu Dr. M.G.R Medical University, Chennai for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2014.

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I, **DR.N.SANGARA NARAYANAN** solemnly declare that this dissertation titled "***A STUDY ON ROLE OF URINE TRYPSINOGEN – 2 IN DIAGNOSING ACUTE PANCREATITIS***" is a bonafide work done by me in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of my unit chief.

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Place: Chennai.
Date: December 2013 **DR.N.SANGARA NARAYANAN**

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INTRODUCTION

Acute pancreatitis is a very common disorder, with substantial burden on the healthcare system[1]. Acute pancreatitis includes wide spectrum of disease varying from mild self-limiting symptoms to fulminant multi organ failure and high mortality. The overall mortality rate is 3-10%, wherein 11-30% of cases are with severe disease manifested as pancreatic necrosis.

Since 1974, several scoring systems have been developed clinically and radiologically assessing the prognosis of the disease. The rationale behind the assessment of severity is mainly for practical purpose, where mild pancreatitis needs supportive care but severe pancreatitis needs intensive monitoring and it has a guarded prognosis.

CONTENTS

ABSTRACT

A STUDY ON ROLE OF URINE TRYPSINOGEN-2 IN DIAGNOSING ACUTE PANCREATITIS

Introduction

Acute pancreatitis is a very common disorder, with substantial burden on the healthcare system[1]. Acute pancreatitis includes wide spectrum of disease varying from mild self-limiting symptoms to fulminant multi organ failure and high mortality. Serum amylase and serum lipase which are used for the diagnosis of acute pancreatitis are relatively less sensitive and specific and gives a lot of false positive or false negative values. The urinary trypsinogen-2 dipstick test, proposed to be a rapid method for the diagnosis of acute pancreatitis at the earliest, based on the immune-chromatographic method.

Materials and Methodology

- 100 Patients presenting with acute upper abdominal symptoms like pain, vomiting, abdominal distention, admitted in the emergency department of our hospital from January 2013 to November 2013 are enrolled in the study.

- Urine sample were obtained from all the patients and tested with Spot Urine trypsinogen-2 dipstick.

- Serum amylase and serum lipase tests were also simultaneously done in these patients. Patients are also evaluated with (USG) abdomen and (CECT) abdomen ,if required.

- Final diagnosis of acute pancreatitis is made on the basis of clinical picture, serum amylase more than threefold rise and radiological findings.

- Urine trypsinogen-2 dipstick test were compared with serum amylase, serum lipase and imaging studies in patients with final diagnosis of acute pancreatitis

Results

Sensitivity of amylase and lipase was found to be 73.77% and 59.02% respectively, whereas as sensitivity of trypsinogen was found to be 78.69%. Specificity of amylase and lipase was found to be 89.74% and 89.74% respectively, whereas as specificity of trypsinogen was found to be 92.1%.Analysing the data ,it is found that sensitivity and specificity of trypsinogen is higher than the routine investigations. Eventhough it has a low range of sensitivity, its high specificity ensures that the test can be used as a screening test to check the true negative cases.

Conclusion

1. Urine Trypsinogen-2 dip stick test is a simple, rapid, easy, and noninvasive test which can diagnose or rule out, most of the cases of acute pancreatitis.

2. Urine Trypsinogen-2 estimation doesn't require laboratory facilities. It is undertaken almost instantaneously (within 5 minutes) as opposed to serum amylase and lipase, results for which may require an hour to get back to the physician.

3. The urinary trypsinogen-2 test could be used as a screening test for acute pancreatitis.

4. Modification of the cutoff point of this assay increases the specificity to the point where it can be used for diagnosis.

Qualitative rapid urine trypsinogen-2 test strip is easy to perform. And hence it has been shown to be a reliable and useful screening test for acute pancreatitis in daily practice [12-16], particularly in healthcare units lacking laboratory facilities.

Keywords

Acute Pancreatitis, Serum Amylase, Serum Lipase, Urine Trypsinogen-2.

INTRODUCTION

Acute pancreatitis is a very common disorder, with substantial burden on the healthcare system[1]. Acute pancreatitis includes wide spectrum of disease varying from mild self-limiting symptoms to fulminant multi organ failure and high mortality. The overall mortality rate is 3-10%, wherein 11-30% of cases are with severe disease manifested as pancreatic necrosis.

Since 1974, several scoring systems have been developed clinically and radiologically assessing the prognosis of the disease. The rationale behind the assessment of severity is mainly for practical purpose, where mild pancreatitis needs supportive care but severe pancreatitis needs intensive monitoring and it has a guarded prognosis.

The key to reduce the mortality and morbidity of the disease is early detection and appropriate management. An ideal diagnostic method should be able to differentiate between patients with mild & severe disease, easy usability, widely available and should be accurate, and with low inter-observer variability. It should be able to detect early disease ,so that patient before developing potential complications,could be monitored and treated, if possible empirically.

Serum amylase and serum lipase which are used for the diagnosis of acute pancreatitis are relatively less sensitive and specific and gives a lot of false positive or false negative values. Various scoring systems are being used in acute pancreatitis to predict the severity and outcome of the disease. There is no single comprehensive test to aid in early and accurate detection of acute pancreatitis.

The urinary trypsinogen-2 dipstick test, proposed to be a rapid method for the diagnosis of acute pancreatitis at the earliest, based on the immune-chromatographic method.

REVIEW OF LITERATURE

HISTORY OF THE PANCREAS

- ***Herophilus***, a Greek anatomist cum surgeon, first discovered the pancreas, in 336 BC ,on the Asiatic side of the Bosporus, Chalcedon[2].

- The word pancreas first mentioned in the writings of **Eristratos** (310-250 B.C.). Then Four hundred years later, ***Rufus***, an anatomist cum surgeon of Ephesus, termed the name **"pancreas".** Written in Greek , the word quotes **"pan: all, kreas: flesh"[2].**

- **Galen** (138-201 AD)a Romen physician, and "Physician to the Gladiators", said that the pancreas serves as a cushion, protecting the large blood vessels, lying behind it[2].

- In March 2, 1642, **Johann Georg Wirsüng,** a German, discovered the pancreatic duct, at San Francisco Monastery, Padua, Italy. But it was named by his colleague as "The Duct of Wirsüng"[2]. The duct enlarges at the terminal point as the papilla, which projects into the second part of duodenum, was first

described by Vater in 1720. In 1734,Santorini, described the accessory duct,that bears his name.

- In 1869, **Paul Langerhans** ("Junior"), a student of -the famous Berlin Institute of Pathology, headed by the eminent Professor, **Rudolph Virchow,** described the pancreatic islets[2],which was the first histologic description of the pancreas.

- In 1893, **Laguesse** suggested that the islet cells produce a hormone. In 1909 **Jean de Meyer** suggested the name 'insulin' for this hormone.

- **Eugene Lindsay Opie** (1873-1971) was able to show the association between diabetes and failure of the islet cells and in 1901, proposed his "common channel" hypothesis[3].

- In 1908, **Julius Wohlgemuth,** Berlin, devised a method to measure the serum amylase concentration ("diastase"), which was found to be useful in diagnosing acute pancreatitis, prior to laparotomy or autopsy[2].

- Since 1898, many surgeons undertook various steps for the resection of tumors of ampulla and head of the pancreas. ***Allen O. Whipple*** (1881-1963), son of American missionaries, Persia, was

recognized as the ***"Father of Pancreatic Surgery"*** for his successful single stage surgery in pancreatic head tumors[2].

- In 1963, the first Marseilles Symposium favored the development of classification system for pancreatitis. This was revised in 1984; at the second Marseilles Symposium.

- Finally, at the Atlanta Symposium, in 1992, clinically oriented classification system was established for acute pancreatitis.

- Although the disease now classified as acute pancreatitis has been known from antiquity, it is only at mid-19th century, the importance of pancreas and its severity became evident. In 1889, Fitz presented the clinical and pathology of acute pancreatitis. Moynihan in 1925 described "the most terrible of all the calamities which occur in relation with the abdominal viscera" as acute pancreatitis[4, 5].

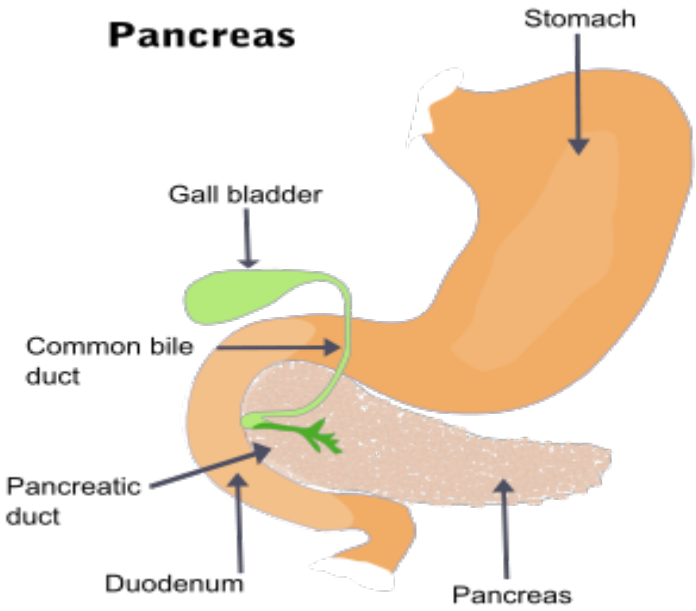
Gross Anatomy

The pancreas, a retroperitoneal organ , extends from the C-loop of the duodenum to the splenic hilum in a oblique manner [7].

The pancreas lies behind the stomach, roughly in the Trans pyloric plane. The gland weighs approximately 80gm, varying from 75 – 125gm and measures 15 to 22 cm length in adults[7].

The pancreas has four parts[7, 8]:

- The head including the uncinate process,
- The neck,
- The body and
- The tail.



The head lies within the duodenal C- loop .It overlies the second lumbar vertebral body and the inferior vena cava(IVC), with the aorta lying beneath the neck of the gland. The right renal artery and the renal veins lie posteriorly behind the head of the pancreas. Coming off ,the side of the head of pancreas, and passing to the left , is the pancreatic uncinate process.

The neck of pancreas lies anterior to the portal vein. Behind the pancreatic neck , the superior mesenteric vein and the splenic vein join to form the portal vein. The inferior mesenteric vein(IMV) forms the tributary of the splenic vein. Sometimes, the IMV drains into the SMV or with the superior mesenteric-portal venous junction, forming a trifurcation. The common bile duct(CBD) lies within a groove in the head of the pancreas, until joining the main pancreatic duct. Both the ducts, join to form the ampulla of Vater, opening into the 2^{nd} part of the duodenum.

The pancreatic body and tail lies anterior to the splenic artery and its vein. The splenic vein lies in a groove, draining multiple pancreatic venous branches. These venous branches must be ligated to perform a spleen-sparing distal pancreatectomy. Along the postero superior edge of the pancreatic body and tail, lies the splenic artery , parallel to the

vein. The splenic artery is highly tortuous. The pancreatic body is covered by the peritoneum, the gastrocolic omentum. On dividing the gastrocolic omentum ,the body and tail of the pancreas can be visualized at the floor of the lesser sac, just posterior to the stomach. It is in this area pancreatic pseudocysts commonly develop , in relation to the posterior aspect of the stomach , allowing drainage of the cyst to the stomach. The transverse mesocolon base ,attaches to the inferior margin of the body and tail of pancreas.

The body of pancreas overlies the aorta, near the origin of the superior mesenteric artery. Blunt antero-posterior trauma can compress the neck of the pancreas against the spine of L1 and L2, causing injury to the pancreatic parenchyma and the duct.

Pancreatic Ductal Anatomy:

Pancreatic duct anatomy and its variations can be understood by knowing the embryology of pancreas. It is formed by the fusion of a ventral bud and a dorsal bud[9].

- The duct from the smaller ventral bud, arises from the hepatic diverticulum, connects directly to the CBD.

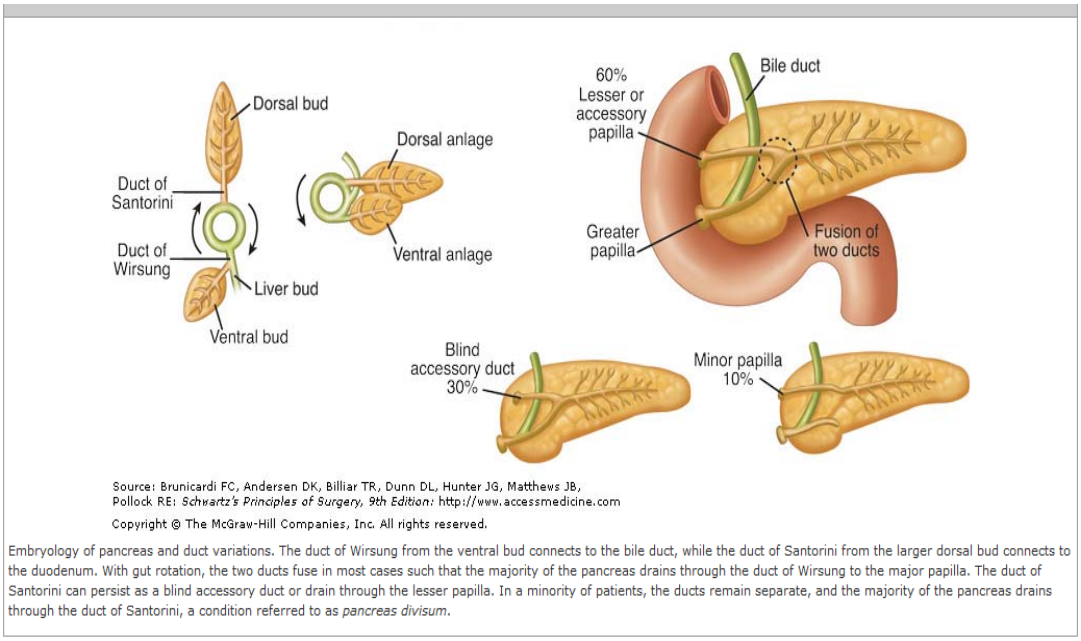
- The duct from the larger dorsal bud, arise from the duodenum.

The ventral anlage duct becomes the duct of Wirsung, and the dorsal anlage duct becomes the duct of Santorini. The ducts from each anlage fuse together, in the pancreatic head such that, most of the pancreas drains through the main pancreatic duct (MPD) or the Wirsung.

The common channel length is often variable. In one third of the patients, the CBD and MPD remains separate till joining the papilla; in another third the two ducts may merge at the papilla, and in the remaining third few millimeters of true common channels persist.

The duct of Santorini, persist as the lesser pancreatic duct.It drains into the duodenum through the lesser papilla,lying proximal to the major papilla. In approximately 30% of patients, the Santorini duct ends as a blind accessory duct . In 10% of patients, the ducts of Wirsung and Santorini , fail to fuse with each other. This ends up with the majority of drainage via the duct of Santorini and lesser papilla. The pancreatic head and uncinate process, drains via the duct of Wirsung and major papilla. This normal variant, occuring in 10% of patients, is referred to as *pancreas divisum*. In a minority , the lesser papilla can't be able to handle the flow of pancreatic juices . This relative outflow

obstruction resulting in pancreatitis,is treated by sphincteroplasty of the minor papilla.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition*: http://www.accessmedicine.com

Embryology of pancreas and duct variations. The duct of Wirsung from the ventral bud connects to the bile duct, while the duct of Santorini from the larger dorsal bud connects to the duodenum. With gut rotation, the two ducts fuse in most cases such that the majority of the pancreas drains through the duct of Wirsung to the major papilla. The duct of Santorini can persist as a blind accessory duct or drain through the lesser papilla. In a minority of patients, the ducts remain separate, and the majority of the pancreas drains through the duct of Santorini, a condition referred to as *pancreas divisum*.

The MPD is normally 2 - 3 mm in diameter. The MPD pressure is about twice that of the CBD, which prevents the bile reflux into the pancreatic duct.

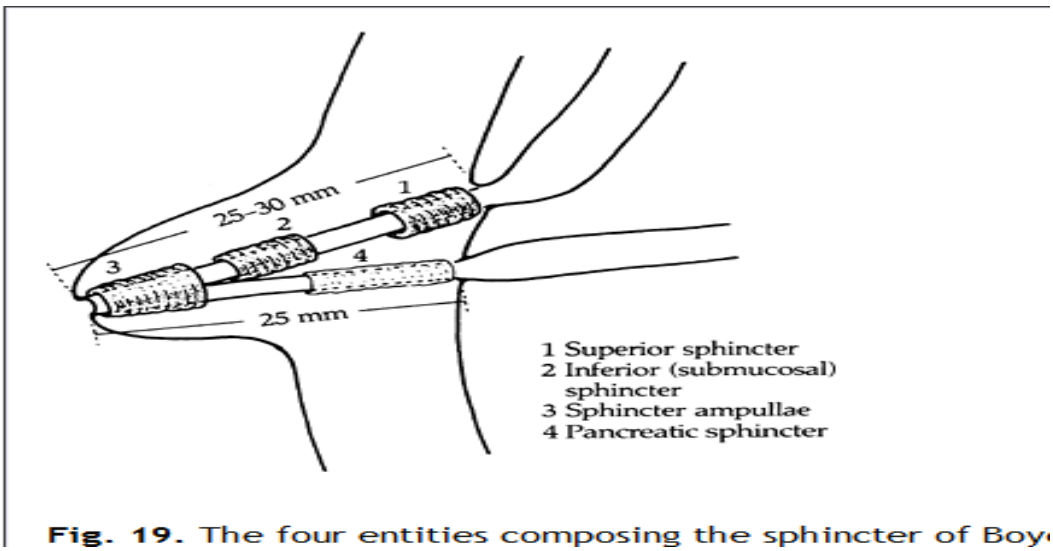


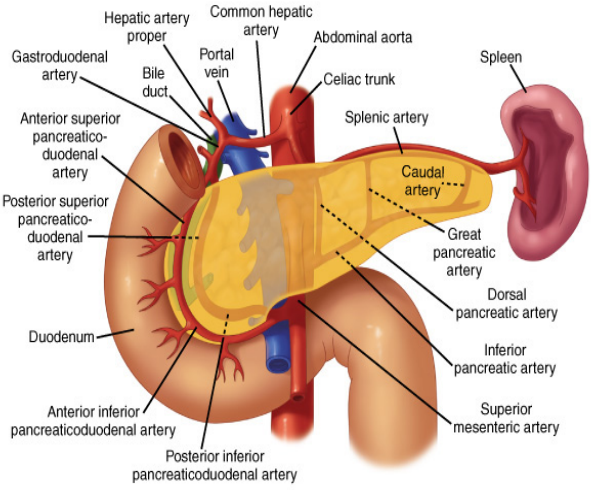
Fig. 19. The four entities composing the sphincter of Boy

The ampullary muscle fiber forms the sphincter of Oddi, controling the biliary and pancreatic secretions into the duodenum. Both hormonal and neural factors regulate the sphincter. When the accessory pancreatic duct or lesser duct opens into the duodenum, a lesser papilla is identified 2 cm proximal to the major papilla.

Arterial supply

The pancreas derives its arterial supply from the celiac axis and the superior mesenteric artery[7, 8].

The coeliac axis gives the common hepatic artery, giving rise to the gastroduodenal artery ,continuing as the hepatic artery proper. The gastroduodenal trunk continues as superior pancreatico-duodenal artery, branching into the anterior and posterior divisions. The superior mesenteric artery, behind the neck of pancreas, gives off the inferior pancreatico-duodenal artery, branching into the anterior and posterior divisions.



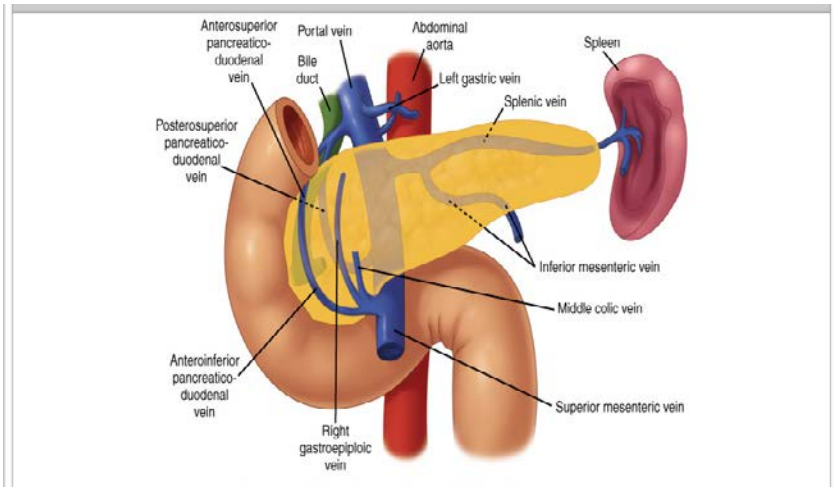
Arterial supply to the pancreas. Multiple arcades in the head and body of the pancreas provide a rich blood supply. The head of the pancreas cannot be resected without devascularizing the duodenum unless a rim of pancreas containing the pancreaticoduodenal arcade is preserved.

The superior and inferior pancreatico-duodenal arteries anastomose within the pancreatic head, along the medial aspect of the C-loop of duodenum, forming an arcade,giving off numerous branches to the duodenum and the pancreatic head. Therefore, it is impossible in resecting the pancreatic head, without devascularizing the duodenum.

The pancreatic body and tail are supplied by splenic artery branches. They are the dorsal (the transverse pancreatic artery), great, and caudal pancreatic arteries. These arteries form an arcade within the pancreatic body and tail, which accounts for the organs rich blood supply.

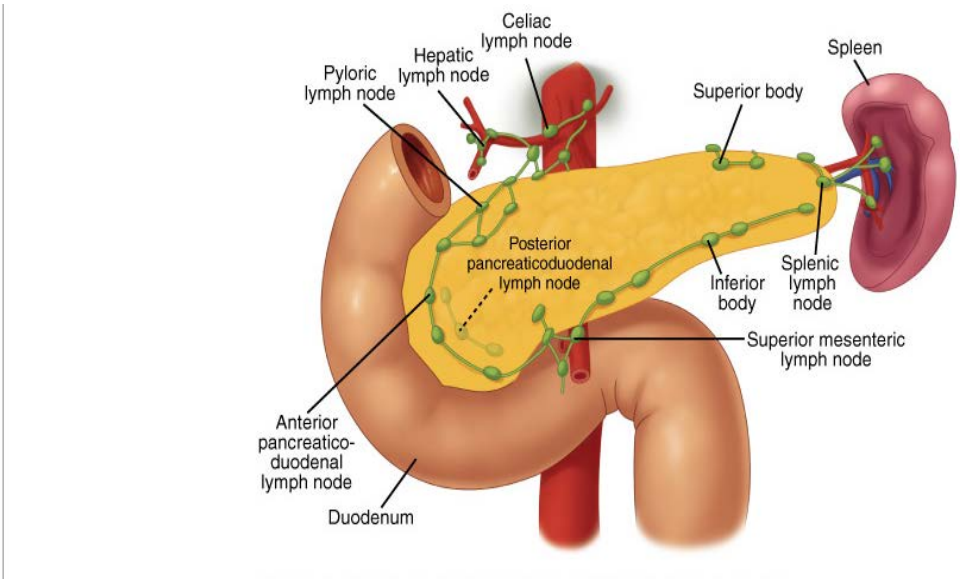
Venous drainage

The venous drainage follows the pancreatic arterial supply[7, 8]. The veins are usually superficial to the arteries within the parenchyma of the pancreas, forming an anterior and posterior venous arcade. The superior veins draining into the portal vein and the posterio inferior vein draining into inferior mesenteric vein. The antero-inferior pancreaticoduodenal vein, joins the right gastro-epiploic vein and the middle colic vein, forming a common venous trunk, draining into the superior mesenteric vein(SMV). Traction on the transverse colon, during colectomy can tear these veins, making control tedious,as they retract into the parenchyma. Numerous small venous branches, from the pancreatic parenchyma drain directly into the lateral and posterior aspect of the portal vein. The body and tail of the pancreas drains into the splenic vein.



Lymphatic drainage

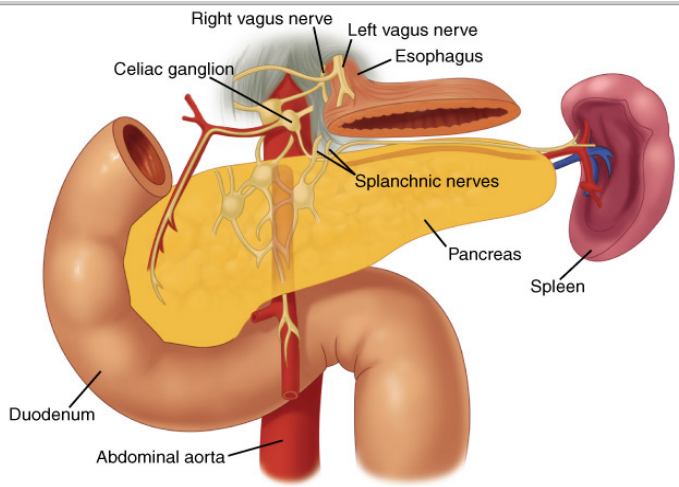
The pancreas has a rich lymphatic drainage and follows the venous drainage[7]. It is due to the diffuse lymphatic drainage, pancreatic cancer presents with positive lymph nodes and a high local recurrence . Lymph nodes are palpated, along the posterior aspect of pancreatic head, in the pancreaticoduodenal groove, along the inferior border of the pancreas, along the hepatic artery ascending into the portahepatis, and along the splenic artery and vein. The pancreatic lymphatics also communicates with lymphatics in the transverse mesocolon and the mesentery of the proximal jejunum. Tumors in the body and tail, often metastasize to these nodes.



Nerve supply

The pancreas is innervated by both sympathetic via splanchnic nerve & parasympathetic via vagus nerve[7, 8]. The acinar cells ,which are responsible for exocrine secretion and the islet cells,which are responsible for endocrine secretion are innervated by both the systems. The parasympathetic system stimulates the endocrine and the exocrine secretion and the sympathetic system inhibits the secretion. The pancreas is also innervated by neurons that secrete amines and peptides, such as somatostatin, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and galanin.

The pancreas also has afferent sensory fibers, which are responsible for the intense pain in advanced pancreatic cancer and pancreatitis. Interrupting these somatic fibers travelling towards the celiac ganglion can stop the transmission of pain sensation in the pancreatic disease.



Innervation of the pancreas. The pancreas has a rich supply of afferent sensory fibers that travel superiorly to the celiac ganglia. Interruption of these somatic fibers with a celiac plexus block can interfere with transmission of pancreatic pain.

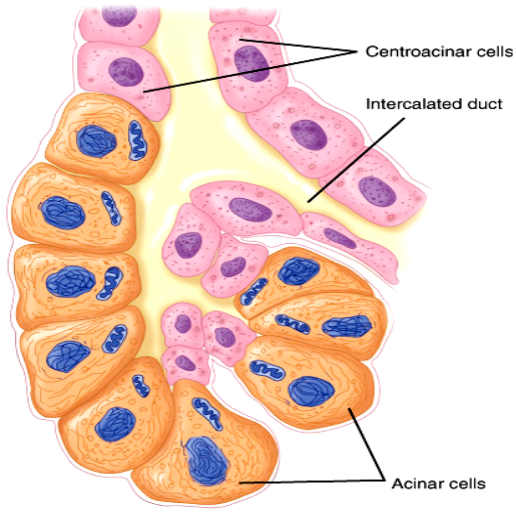
Histology

Pancreas has both exocrine and endocrine glandular tissues. The exocrine pancreas consists of acinar glands, whereas the endocrine part consists of islets of Langerhans[10].

The pancreas contains 85% of exocrine gland, 10% of extracellular matrix, and 4% of blood vessels & the major ducts, and only 2% of endocrine tissue[11]. Thus the endocrine and exocrine pancreas is thought to be functioning separately, but coordinated well for regulating the feedback system of digestive enzyme and hormone secretion.

The acinar cells, so named because they are clustered like grapes on the stem. The main duct ramifies into intralobular and interlobular

ducts, ductules and finally acini, that secretes into a centrally located acinar space that communicates with the main pancreatic duct. Histologically, acinar cells have a high content of endoplasmic reticulum with apically located eosinophilic zymogen granules. The cells lining the main pancreatic duct are tall columnar cells, and many contain mucin granules. With progression from the large ducts to the smaller intralobular and interlobular ducts, the lining cells become flatter, assuming a cuboidal configuration, and mucin granules are no longer seen. Centroacinar cells, located at the junction between ducts and acini, resemble acinar cells in size and shape but lack zymogen granules[7].



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition*: http://www.accessmedicine.com

Acinar cell. Zymogen granules fuse with the apical membrane and release multiple enzymes to digest carbohydrates, proteins, and fat.

The islets of Langerhans are distributed throughout the pancreas. Capillaries draining the islet cells drain into the portal vein forming a pancreatic portal system.

Surgical physiology

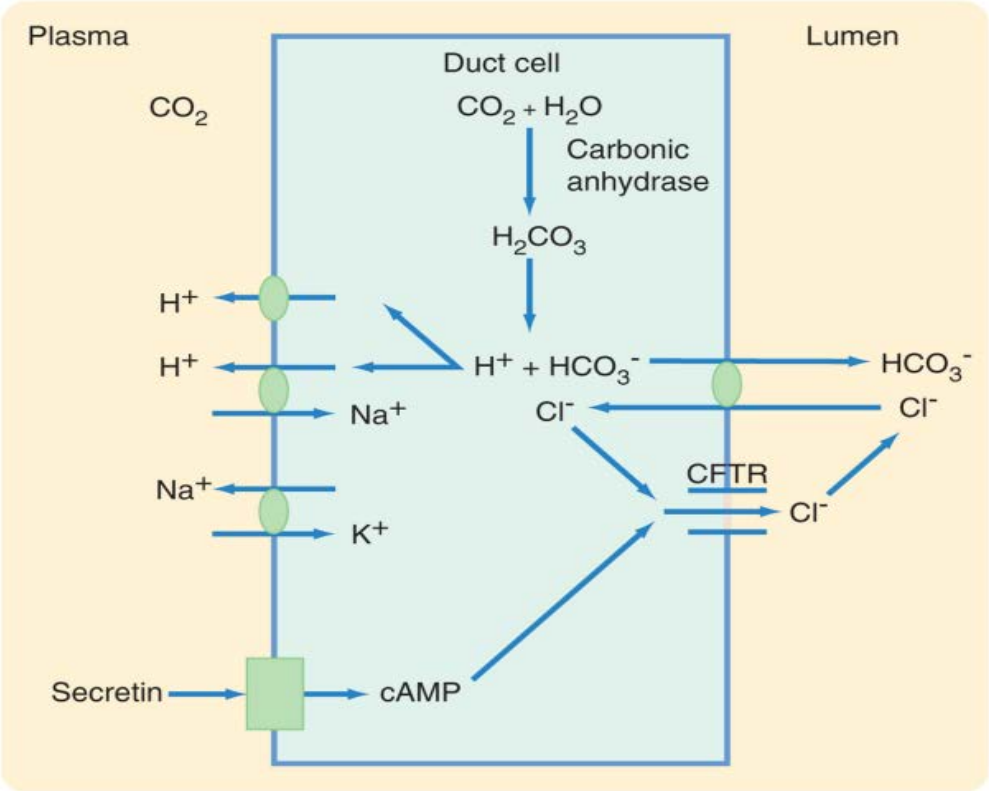
In response to a meal, the duodenal mucosa releases the hormone secretin ,which stimulates the pancreas to secrete an alkaline bicarbonate-rich enzymes with a pH of 8.4. Cholecystokinin-pancreozymin (CCK), released from the duodenal mucosa , produces no increase in the volume of secretion, but is responsible for enzyme secretion. Vagal stimulation increases the volume. Approximately 6 - 20 gm of digestive enzymes enters the duodenum each day[7, 8].

Exocrine Pancreas

The pancreas secretes about 500 to 800 mL of odourless, colourless, isosmotic, alkaline, pancreatic juice daily[7]. Pancreatic juice is made up secretions from ductal and acinar cells, which are responsible for digestion of carbohydrate, protein, and fatty foods.

Pancreatic amylase, the only enzyme secreted in the active form. All other enzymes are secreted in the proenzymes form.. Trypsinogen has several isoforms and a missense mutation on the cationic

trypsinogen, results in intrapancreatic activation of trypsinogen[12] accounting for the hereditary pancreatitis.



Endocrine Pancreas

In adults,about 1 million pancreatic islet cells are present with sizes from 40 – 900 µm. Larger cells lie close to major arterioles and smaller cells are embedded deeply in the parenchyma.

Most islets contain five major types of cells:

1. α cells - secretes glucagon(20%)
2. β cells - secretes insulin(75%)
3. δ cells - secretes somatostatin
4. ε cells - secretes ghrelin and
5. PP cells - secretes pancreatic polypeptide.

Table 33-2 Pancreatic Islet Peptide Products

Hormones	Islet Cell	Functions
Insulin	β (beta cell)	Decreased gluconeogenesis, glycogenolysis, fatty acid breakdown, and ketogenesis
		Increased glycogenesis, protein synthesis
Glucagon	α (alpha cell)	Opposite effects of insulin; increased hepatic glycogenolysis and gluconeogenesis
Somatostatin	γ (delta cell)	Inhibits GI secretion
		Inhibits secretion and action of all GI endocrine peptides
		Inhibits cell growth
Pancreatic polypeptide	PP (PP cell)	Inhibits pancreatic exocrine secretion and section of insulin
		Facilitates hepatic effect of insulin
Amylin (IAPP)	β (beta cell)	Counterregulates insulin secretion and function
Pancreastatin	β (beta cell)	Decreases insulin and somatostatin release
		Increases glucagon release
		Decreases pancreatic exocrine secretion
Ghrelin	ε (epsilon cell)	Decreases insulin release and insulin action

IAPP = islet amyloid polypeptide.

ACUTE PANCREATITIS

Definition:

Acute pancreatitis is “an inflammatory disease, associated with, little or no fibrosis of the pancreas”, several initiating factors including gallstones, alcohol, trauma, and infections, and, rarely hereditary[7].

Etiology of acute pancreatitis:

Acute Pancreatitis is multifactorial. On the basis of the worldwide data, the most common cause is gallstones, accounting for 45 percent of cases. Alcoholism is the second common cause**,** accounting for 35 percent of cases. In a study done at New Delhi, India, gall stones and alcoholism were found to be the cause of pancreatitis in 49% and 23.6% of cases, respectively[13].

The disease occurs at a higher rate in young men and old women. Females are more prone to have gall stone pancreatitis and males are more prone to have alcohol induced pancreatitis[14].

CAUSES OF ACUTE PANCREATITIS[7]:

Alcohol

Biliary tract disease

Obstructive causes:

- Choledocholithiasis
- Ampullary carcinoma or pancreatic malignancy
- Papillary obstruction by worms/foreign bodies
- Pancreas divisum with minor duct obstruction
- Choledochocele
- Duodenal diverticula at periampullary region
- Spasm of sphincter of Oddi

Toxins or drugs:

- **Toxins:-** ethanol/methanol, scorpion sting, organo phosphorous compounds

- **Drugs:-** Definite Cause

  5-Aminosalicylate (ASA)

  6-Mercaptopurine (6-MP)

  Azathioprine

Cytosine arabinoside (cytarabine)

Didanosine

Diuretic agents

Estrogens, etc.

Trauma:

- External injury to the abdomen.
- Iatrogenic injury- postoperative trauma, post ERCP, post endoscopic sphincterotomy and manometry of sphincter of Oddi

Metabolic abnormalities:

- Hypercalcemia
- Hypertriglyceridemia

Inherited conditions

Infection:

- Parasitic:- ascariasis, Clonorchis sinensis
- Viral:- mumps,HIV,EBV,CMV rubella, hepatitis, coxsackie B, echo virus, adenovirus varicella.

- Bacterial: - Camphylobacter jejuni ,mycoplasma pneumoniae, , Myco. tuberculosis, legionella pnemophila, MAC, leptospiral infection

Vascular causes:

- hypo perfusion causing ischemia (e.g., after major cardio-vascular surgery)
- Athero-embolism
- Vasculitis- SLE, PAN, malignant hypertension

Miscellaneous causes:

- Peptic ulcer penetration
- Cystic fibrosis
- Crohn's disease
- Reye's syndrome
- Hypothermia

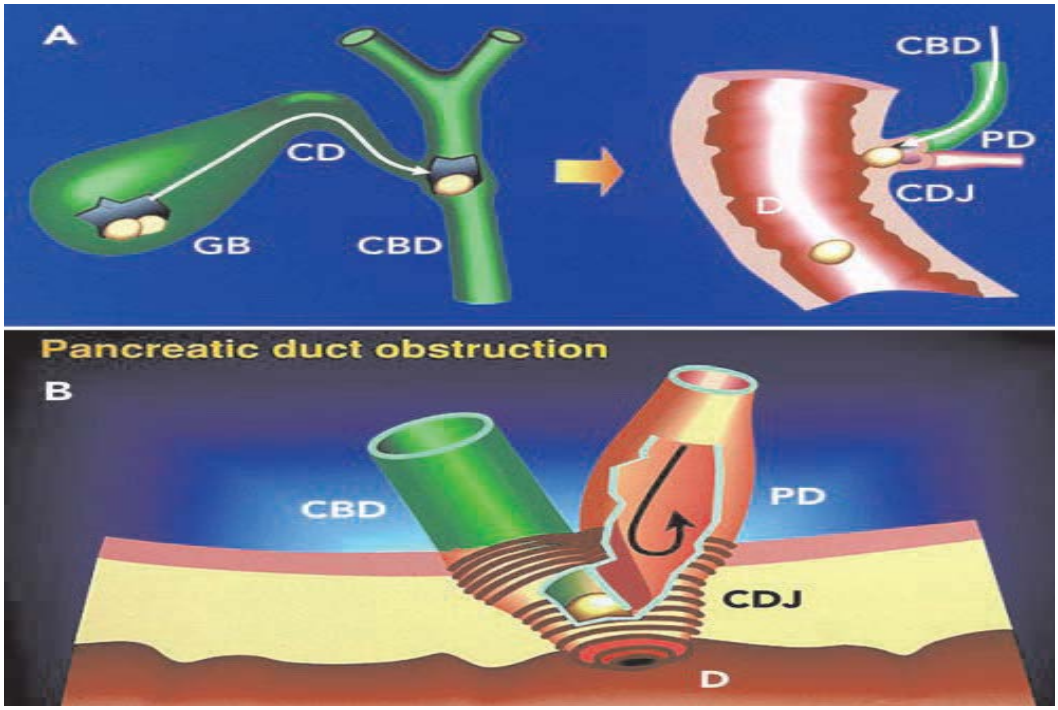
Gall stones

Gall stone disease, the leading cause of acute pancreatitis (30-60%). Women are more commonly affected , and incidence varies between 50 to 60 yrs of age[14].

In 1901, Opie, Johns Hopkins Hospital , Baltimore, reported a case of impaction of gallstone at the ampulla of Vater ,following an autopsy of a patient (operated on by Halsted) who died, due to gallstone induced pancreatitis[3].He suggested that the stone might have caused an outflow obstruction of the common 'biliopancreatic channel', which led him to propose the "common-channel hypothesis[3]",which states that a blockage below the junction of the common ducts, would cause bile to back flow into the pancreas to cause damage. Although this theory was originally favored, most observers now believe that, it is the stone-induced pancreatic duct obstruction and ductal hypertension, rather than bile reflux that triggers acute pancreatitis.

Opie's hypothesis dominated much of the twentieth century, but it is regarded as a myth today. Lerch et al. demonstrated that pancreatic duct obstruction alone causes necrotizing pancreatitis.

Another proposed mechanism is that, passage of a gallstone through the sphincter of Oddi, renders it incompetent, allowing the duodenal juice reflexing into the pancreatic ductal system.



Microlithiasis (occult gall stones/biliary sludge)is also a well-known cause of acute pancreatitis. Microlithiasis is diagnosed by Biliary microscopy & endosonography.

Alcohol

Alcohol, the second most common etiological agent,accounts for 30% of cases. The disease can recur with continuous abuse of alcohol.

Various theories have been put forward[7, 8]:

1. Alcohol consumption alters lipid metabolism. A transient hyperlipidemic state, causing hypertriglyceridemia with

generation of fatty acids and their metabolites, that can injure the pancreas.

2. Alcohol causes intra pancreatic generation of oxygen free radicals, which can injure the pancreas.

3. It promotes secretion of pancreatic juice with high proteolytic content and low enzyme inhibitor content. Enzyme activation can theoretically occur in these conditions, causing pancreatic injury.

4. "***Secretion with blockage***" mechanism: Ethanol produces sphincter of Oddi spasm , leading to ductal hypertension. Ethanol is a metabolic toxin to the acinar cells, interfering with enzyme synthesis and secretion.

5. Secretion of enzyme-rich fluid with precipitation of protein and calcium within this protein matrix, causes multiple ductal obstructions. Continued secretion can cause pressure to buildup with the formation of intra-ductal plugs, which cause ductal obstruction and ductal hypertension.

6. Ethanol causes focal ischemic injury to the gland,with transient decrease in the pancreatic blood flow.

Hyperlipidemia

It is responsible in 1.5-4 % of cases. Triglyceride level > 1000 mg/dl increases the likelihood of developing pancreatitis. Hyperlipidemia type I, IV and V can cause pancreatitis. Lipase liberates large amounts of toxic fatty acids into the pancreatic microcirculation[8] ,leading to endothelial injury and ischemic injury.

Hypercalcemia

Hypercalcemia, secondary to hyperparathyroidism or any other cause can cause acute pancreatitis. The mechanism most likely is hyper secretion and formation of calcified stones intra ductally.

Iatrogenic Pancreatitis

Acute pancreatitis is associated with a number of surgical procedures and postoperatively with Billroth II gastrectomy and jejunostomy, where increased intraduodenal pressure, can cause backflow of the enzymes into the pancreas.It also occurs in association with surgery with low systemic perfusion. Atheromatous emboli or ischemia can cause pancreatic injury. Most commonly, endoscopic retrograde cholangio pancreatography (ERCP) results in pancreatitis in

2 to 10% of patients, due to direct injury and/or intraductal hypertension.

Tumours

About 1 to 2% of cases of acute pancreatitis, may harbour pancreatic malignancy. Periampullary tumor may present as pancreatitis ,which would be the first clinical sign.

Drugs

For practical reasons, it is often difficult to implicate a drug as the cause of pancreatitis. A drug is considered to be a cause, if the pancreatitis-like illness resolves with its discontinuation.

Infections

Though mumps, coxsackie virus, and *Mycoplasma pneumoniae* are believed to be capable of inducing acute pancreatitis, none of these have been isolated, from a diseased pancreas. The antibody titres to mumps and coxsackie virus are elevated in about 30% of cases with acute pancreatitis . However, this elevation may be an anamnestic or nonspecific response to pancreatitis.

Miscellaneous Causes

Infestations by Ascaris lumbricoides and Clonorchis sinensis, cause Oriental cholangitis, associated with cholangiocarcinoma and obstructing the pancreatic duct.

A dominant gene mutation with Mendelian inheritance, is seen in hereditary pancreatitis. Whitcomb and associates, described mutations in the cationic trypsinogen gene *PRSS1*, which results in acute pancreatitis.

20 to 45% of patients with pancreas divisum (unfused ducts of Wirsung and Santorini) develop pancreatitis. The failure of procedures in improving the pancreatic drainage , and reducing attacks of pancreatitis, contradicts pancreas divisum as an etiologic factor[12].

Finally, no cause could be attributed to some episodes of pancreatitis, and these groups are referred to as *idiopathic pancreatits*[15].

Pathophysiology

Acute pancreatitis is triggered by digestive enzymes, which got activated inside acinar cells. The ultimate severity depends upon the event, that subsequently occurs following the acinar cell injury. The

events are activation and recruitment of inflammatory cell, synthesis and release of cytokines and other inflammatory mediators. Large amounts of liberated digestive enzymes however overwhelm the system as a whole.

There are three reasons for this theory[7, 15]:

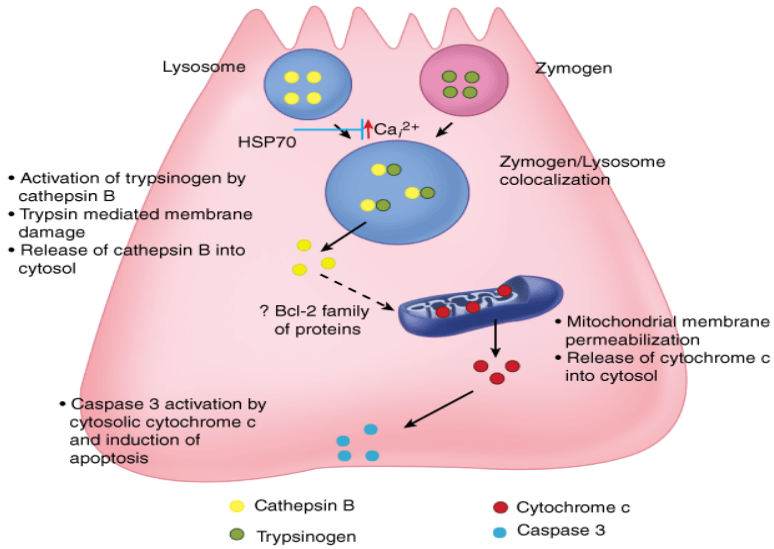
(a) Activated enzymes of the duodenum digest the pancreatic tissue.

(b) Activated enzymes are found within the pancreas, during acute pancreatitis.

(c) The histology of pancreatitis is suggestive of a coagulative necrosis.

According to "***colocalization hypothesis***" ,digestive enzymes are localized in the cytoplasmic vacuoles. These vacuoles also contain the lysosomal hydrolase Cathepsin B, known to activate trypsinogen[7]. Recent studies suggest that, cathepsin B inhibition by specific inhibitor, CA-074me, protects against the intra-acinar cell trypsinogen activation, and hence pancreatitis. These findings suggest that, the trypsinogen is activated because it erroneously colocalises in cytoplasmic vacuoles with cathepsin B.

Recent studies suggest that, activated trypsin (appears similar to autophagic vacuoles), mediates the permeability of these organelles and release their contents into the cytosol.



Inside the cytosol, Cathepsin B initiates apoptotic cell death by permeabilizing mitochondrial membranes.

FACTORS INFLUENCING THE PANCREATIC SEVERITY:

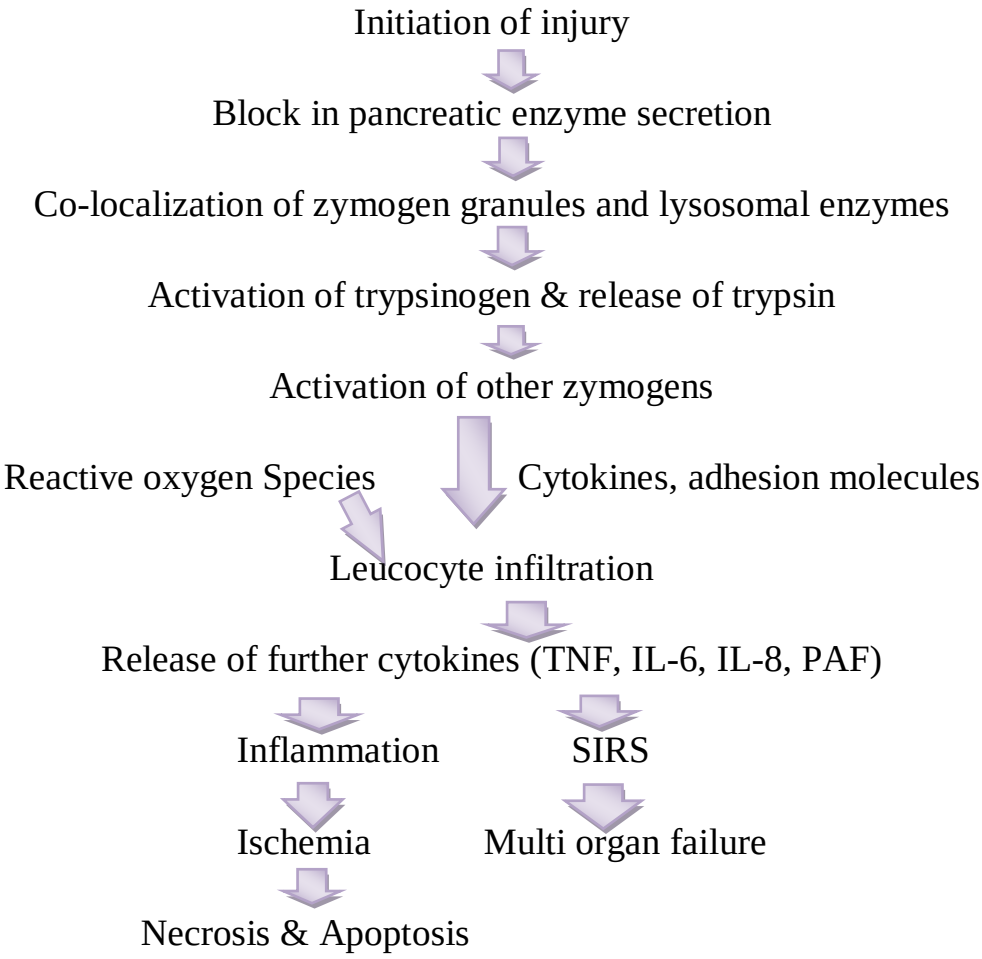
The severity of acute pancreatitis varies significantly. Some have a mild form of disease, that is self-limiting, while others suffer a severe form and sometimes lethal attack. Factors determining the severity of pancreatitis are multifactorial. Their identification is of considerable therapeutic significance, because their manipulation may decrease the morbidity and mortality associated with the disease.

In addition to the neutrophils, the pancreatic acinar cells produce inflammatory mediators . The factors compounding with pancreatitis and lung injury include: tumor necrosis factor alpha, monocyte chemotactic protein-1, Mob1, interleukin-1β (IL-1β), platelet activating factor, substance P, adhesion molecules [intercellular adhesion molecule-1 (ICAM-1) and selectins], IL-6, 8, 10, C5a, the CCR1 receptor, granulocyte-macrophage colony-stimulating factor, macrophage migration inhibitory factor, COX-2, prostaglandin E1, nitric oxide (NO) and reactive oxygen species. Heat shock proteins are protective in pancreatitis The balance between the pro-inflammatory and anti-inflammatory factors,decide the severity of pancreatitis and lung injury[7].

Several therapeutic regimens aimed at reducing the inflammatory response. They include anti–tumor necrosis factor alpha antibody, IL-1 receptor antagonist, IL-10, anti-ICAM-1 and anti-CD3 Ab, rPAF acetyl hydrolase, and the calcineurin antagonist FK506[8].

Recent studies also indicate that , Toll-like receptor 4 (TLR4) is significant in determining the severity of acute pancreatitis. The TLR4,by initiating a complex signaling pathway, interacts with lipopolysaccharides, resulting in a proinflammatory response. However, this effect appears independently of lipopolysaccharides. TLR4 antagonists would be a good therapy, against pancreatitis[15].

An alternate approach to prevent or reduce the severity of pancreatitis is, to inhibit intrapancreatic trypsinogen and NF-κB activation, the two events which occurs early in pancreatitis. Prior thermal (and arsenite) & water immersion stress, up regulates hsp 70 and 60, respectivel. Thus preventing cerulein-induced trypsinogen activation,and hence inhibiting cerulein-induced NF-κB activation , hence protective in pancreatitis[7, 8].



Schematic representation of the mechanisms of pathogenesis of acute pancreatitis[16]

Clinical presentation:

The clinical presentation, diagnosis, and management of an acute attack of pancreatitis looks similar in both acute or chronic pancreatitis. Acute pancreatitis can mimic like acute abdomen, and should never be excluded in differential diagnosis[8].

Abdominal pain, nausea, and vomiting present as the predominant symptoms. Each episode begins with severe pain. The cardinal symptom is usually epigastric pain. The pain was described as "knifing" or "boring through" to the back, relieved by leaning forward(***Mohmadian prayer position***). Pain starts 12-48 hours after a bout of alcohol, or after a large meal in case of gall stone pancreatitis. Pain became generalized once peritonitis has been sets in[8, 15].

Painless pancreatitis is seen in Peritoneal dialysis, post-operative situations, legionnaire's disease.

If patient develops generalized paralytic ileus, abdominal distension and vomiting can occur. The vomiting may lead to gastro esophageal tears (i.e., Mallory-Weiss syndrome) and upper gastrointestinal bleeding. Vomiting is more intense in necrotizing pancreatitis than in edematous pancreatitis. Although vomiting and

retching may be relieved by passage of a nasogastric tube, the pain usually persists even after gastric decompression.

Fever is an important sign. Fever presenting during first week ,is due to acute inflammation, mediated by cytokines. Fever during the second or third week, is due to infected pancreatic necrosis.

Physical Findings:

The patient may have tachycardia , tachypnoea , hypotension, and hyper thermia[7, 8].Abdomen findings include Voluntary and involuntary guarding,with decreased or absent bowel sounds . Unless pseudocyst develops ,pancreatitis does not present with mass. Abdomen may be distended due to pancreatic acites. Acute pancreatitis may be associated with left sided pleural effusion.

With increasing severity, there is sequestrations of fluid in the retro peritoneum leading to life threatening intravascular fluid loss,which leads to hemoconcentration. There might be bleeding into the retro peritoneum or peritoneal cavity, which may dissect via the soft tissues, appearing as a bluish discoloration around the umbilicus (Cullen's sign) or in the flanks (Grey Turner's sign) and the inguinal region (Fox's sign)[17]. Neither sign is pathognomonic of AP.

The severe intravascular fluid loss may lead to acute renal shutdown with elevated BUN and creatinine levels. And also there may be hyperglycemia, hypoalbuminemia, and hypocalcemia that are sufficient enough to produce tetany in few cases.

Diagnosis:

The clinical diagnosis is one of exclusion and diagnosis may be difficult ,despite the multiple serological and radiological investigations are available.

Serum pancreatic enzymes:

Serum pancreatic enzyme estimation,the gold standard for diagnosis[18]. The reason is pancreatic acinar cells synthesize, store, and secrete a large amount of digestive enzymes (e.g., amylase, lipase, trypsinogen, and elastase), which gets elevated in acute pancreatitis.

Amylase, lipase, elastase and trypsin were secreted in the blood at the same time, but their clearance differs due to the different sensitivities.

Serum amylase concentration will increase immediately, reaches the peak , within several hours after the onset of disease ,remains raised

for 3 to 5 days and then returns back to normal. No significant correlation has been found, between the level of serum amylase and severity of pancreatitis. Hyperamylasemia is also seen in biliary tract disease, intestinal obstruction, mesenteric ischaemia, acute appendicitis, mumps, parotitis, impaired amylase excretion etc…[18]. In contrast, a patient with acute pancreatitis may even have a normal serum amylase level, because of the interference by lipids, with chemical determination of serum amylase. Urinary amylase clearance increases during pancreatitis; predicting better results than serum amylase. For these reasons, it is recommended to measure the urinary amylase , which usually remain elevated for several days after serum amylase levels have returned back to normal. In patients with severe necrotic pancreatitis , the pancreas may not release large amounts of enzymes .

The serum lipase has been found to be highly sensitive and specific, in diagnosing acute pancreatitis, as there are no other sources of lipase[15, 17]. Total amylase is having a sensitivity of 84%, the serum P- amylase has 95% and lipase has 93%. Specificities for amylase, P-amylase and lipase respectively are- 88%, 93% and 96%, respectively. Thus P-amylase is the enzyme with the higher diagnostic value.

The rise of lipase: amylase has been found to differentiate alcoholic from nonalcoholic pancreatitis. The serum (SGPT) alanine aminotransferase level rise of three or more times above the base-line value has great specificity in diagnosing gallstone pancreatitis.

Immunologic assay like serum trypsinogen or immune lipase are generally less specific than the lipase assay. The increased urinary level of activated peptides, released by trypsinogen, procarboxypeptidase, or prophospholipase activation, may aid in predicting the severity of an attack.

Leucocyte migration and its activation, is considered as a major determining factor of local & systemic complications[8, 15].

Although methemalbumin rise indicates severe pancreatits and a poor prognosis, methemalbumin levels are usually not measured. Circulating levels of several inflammatory mediators and acute phase reactants

(e.g., IL-1, 6, TNF-alpha, and CRP) also increase during pancreatitis, and the magnitude of those increases can be used to predict the severity of an attack. C reactive protein is readily available in all centers and vales > 120mg/L, after 72 hours are closely related to necrotising pancreatitis.

Imaging:

In general, the plain chest and abdominal radiographs can be useful in the management, by identifying other causes for the patient's symptoms (e.g., pneumonia, perforated hollow viscous, mechanical bowel obstruction). Plain abdominal X-ray findings are either generalized or localised ileus (sentinel loop), colon “cut-off” sign or “renal halo” sign. A chest radiograph may show left pleural effusion, elevated left hemi diaphragm or basal atelectasis[17].

Ultrasonography:

Abdominal ultrasound (US) examination is the gold standard for confirmation of gallstones pancreatitis. It is also helpful to detect extra pancreatic ductal dilations & pancreatic edema, swelling, free peritoneal fluid and peripancreatic acute fluid collections (PFCs).It may not be sensitive in about 20% of cases, due to bowel gas interference with the imaging.

CT scan:

The contrast-enhanced computed tomography (CECT), has become gold standard for[17]

- Diagnosis
- Assessing the severity
- Identify the complications associated with acute pancreatitis.

The Balthazar scoring system and other similar grading systems have incorporated various CT findings such as inflammation and fluid collections in & around the pancreas to correlate radiographic appearance with morbidity and mortality[19].

Early CT scans often fail to detect evolving necrosis, which would become well demarcated by 2 to 3 days after the onset of symptoms. The CT scans are not useful in diagnosing necrosis or predicting the severity in the first 24 hours of illness. The sensitivity for identifying pancreatic necrosis using contrast-enhanced CT scan approaches 100%, 4 days from diagnosis. CT scans is useful in the early diagnosis of infected pancreatic necrosis and image guided aspiration of necrosis, when patient not improving clinically or who experience clinical decline. In the patient with moderate renal impairment or allergy to intravenous contrast material, magnetic resonance imagining (MRI) may be useful. MRI has been found to have sensitivity and specificity similar to contrast-enhanced CT, for detecting severe acute pancreatitis.

ERCP should be done in patients with acute pancreatitis , whose clinical course fails to improve despite full intensive care support, and in whom ampullary or common bile duct stone impaction is suspected, based on ultrasonography, or clinical/biochemical signs of cholangitis. It may also be helpful in patients ,with recurrent attacks of acute pancreatitis, without any obvious cause. It is useful in correcting potentially correctable lesions such as CBD stones with impaction, pancreas divisum, ampullary stenosis, pancreatic duct stenosis etc.

Assessment of Severity:

Assessment of mild and severe necrotizing pancreatitis, is the most important thing for providing optimal care to the patient[7]. There are so many predictors available for assessing the severity, which includes early prognostication signs, serum markers, and CT scan[15].

Scoring systems in acute pancreatitis:

The various prognostic scoring systems for assessing the severity will be discussed in detail later.

UK guidelines for the management of AP[20]:

- Diagnosis should be made within 48 hrs. of admission.
- The etiology has to be determined in 80% of cases at least and idiopathic cause should not exceed 20%.
- The serum lipase assay has been preferred over serum amylase assay for diagnosis the acute pancreatitis.
- The contrast enhanced computed tomography has to be preferred over USG for detection of the presence/absence of pancreatitis.

Treatment:

Evolution of an acute attack of pancreatitis occur in two phases, overlapping on each other[15, 17].

The initial phase, lasting for 1 to 2 weeks, involves an acute inflammatory and autodigestive process. It may have systemic effects as well.

The second phase, that may last for weeks or months, is primarily characterized by the development of local complications that are, themselves, the results of necrosis, infection and pancreatic duct rupture.

The initial management of patients with pancreatitis focuses on early establishment the diagnosis, assessing the severity, treating the major symptoms, and haltering the disease progression. The treatment for acute pancreatitis is largely supportive. Since 15-30 % patients develop severe pancreatitis, so each and every patient should be treated aggressively. The main aim of the treatment is ‘allowing rest to the gland’ by oral feed and fluids restriction[21]. The goal of initial management consists of adequate fluid replacement,nutritional support, correction of electrolyte imbalance, and prevention of local & systemic complications.

Management of Pain

Good analgesics should be given to these patients as the pain can be very severe in intensity. Most patients require narcotic analgesics. Meperidine is preferred as morphine induces spasm of the sphincter of Oddi, which can, at least theoretically, worsen biliary pancreatitis.

Fluid and Electrolyte Management

Aggressive fluid resuscitation is important to replenish extravascular, or "third space," fluid loss, which may be considerable. The fluid resuscitation is of utmost importance to prevent systemic

complications, mainly acute renal insufficiency, that may occur with hypovolemia. Transudation of the fluid from intravascular space into the areas of inflammation (i.e., peripancreatic, retroperitoneum and into the pulmonary parenchyma and soft tissues elsewhere in the body) is the principle cause of hypovolemia. Furthermore, studies have shown that inadequate resuscitation may add upon as a significant risk that leads to further pancreatic injury.

Banks and colleagues have showed that, aggressive fluid resuscitation would not prevent the progression of developing pancreatic necrosis. The degree and intensity of monitoring depends upon the disease severity[22].

During the first several days of a severe attack, circulating levels of many proinflammatory factors, including cytokines and chemokines, are elevated. This so-called ***"cytokine storm"***, in many cases, triggers the systemic immune response syndrome, and as a result, the hemodynamic parameters of these patients may resemble those of sepsis associated with other disease states[23]. Heart rate, cardiac output, and cardiac index usually rise, and total peripheral resistance falls. Hypoxemia can also occur as a result of the combined effects of increased intrapulmonary shunting and a pancreatitis-associated lung

injury that closely resembles that seen in other forms of ARDS. Fluid management, though critical, may be difficult when hypovolemia is combined with respiratory failure of ARDS.

Measurement of central filling pressures, using a Swan-Ganz or central venous pressure catheter, can be helpful in guiding fluid management, particularly when hypovolemia is combined with lung injury.

Nasogastric Decompression

The nausea and vomiting of pancreatitis can result in significant fluid as well as electrolyte losses and retching can lead to gastro-esophageal mucosal tears and result in upper gastrointestinal bleeding (i.e., the Mallory-Weiss syndrome). For symptomatic relief and to increase patient comfort, nasogastric decompression may be needed, although the institution of nasogastric drainage does not shown to alter the eventual outcome of an attack[7, 8].

Prophylactic Antibiotics

Infection is a serious complication of acute pancreatitis and is the most common cause of death[17]. It is mostly caused by the enteric bacteria and was seen commonly in necrotizing pancreatitis. Local

infection occurs with pancreatic necrosis, and as time progresses for at least the first 3 weeks,the disease progresses. Aerobic and anaerobic gastrointestinal floras are the primary organisms involved, and infections may be either mono or polymicrobial in nature. The predominant microbes seen were E. coli (35%), Kleb. pneumoniae (25%), Streptococcus (25%), Staphylococcus (15%), and Pseudomonas (10%).The association of high mortality with pancreatic infection has been the rationale behind the use of prophylactic antibiotics widely in patients with pancreatic necrosis. In severe pancreatitis, beneficial effects have been observed with regimens that included imipenem alone, imipenem with cilastatin, metronidazole and third-generation cephalosporin (cefuroxime). Because *Candida* species are common inhabitants of the upper GI tract, *Candida* sepsis and secondary fungal infection of pancreatic necrosis is a risk in severe disease, and many surgeons advocate empirical therapy with fluconazole in severe acute pancreatitis.

The duration of treatment has not defined clearly. A treatment course of 1week to 4 weeks has been recommended commonly, but many of them limit the treatment to 2 weeks[17].

According to the current UK guidelines (Johnson 2005), the duration of antibiotic prophylaxis is 1 to 2 weeks[20].

Nutritional Support

Classically speaking, the enteral feeding should be limited, thereby pancreatic stimulation and further pancreatic injury by the release of proteolytic enzymes can be avoided. Recent data, suggests that such strict limitations of enteral nutrition may have been unnecessary. Most of the severe acute pancreatitis patients found to have prolonged course of illness with hyper catabolic state and ileus that have led to a generous use of parenteral nutrition in them.

The points favoring enteral nutrition are[7, 15]:

- It might feasible, safe, and desirable in severe pancreatitis.
- It has the advantage of avoiding the high cost of total parenteral nutrition (TPN) as well as its associated catheter-related complications.
- The use of enteral nutrition may support intestinal mucosal integrity by avoiding the alteration in intestinal permeability & barrier function as seen with use of TPN.

Treatments of Limited or Unproven Value

In patients who develop severe disease, other treatment modalities may be tried. The antiproteases like gabexate/aprotinin, antisecretory agents like octreotide and anti-inflammatory drugs or PAF antagonists like lexipafant were found to be less useful[15, 17].

Treatment of Early Systemic Complications of Pancreatitis

The pathogenesis and management of the cardiovascular collapse, respiratory failure, renal failure, metabolic encephalopathy, gastrointestinal bleeding, and disseminated intravascular coagulation that complicate severe pancreatitis appear to be identical to those involved when these processes are superimposed on other disease states that are characterized by peritonitis and hypovolemia[8].

Cardiovascular collapse is largely caused by hypovolemia, and its management requires aggressive fluid and electrolyte repletion.

The pulmonary manifestations of pancreatitis include atelectasis and acute lung injury. The latter appears to be similar to the acute lung injury caused by other systemic processes, including septic shock, ischemia and reperfusion, and massive blood transfusion. Management includes good pulmonary toilet combined with close monitoring of

pulmonary function. For many patients, intubation and respiratory support may be required.

Renal failure in pancreatitis is usually prerenal and is associated with a poor prognosis,sometimes requiring hemodialysis.

Stress-induced gastro duodenal erosions account for most of the gastrointestinal bleeding, prophylaxis with antacids, H_2-receptor antagonists, or proton pump inhibitors may be appropriate.

Rarely, massive bleeding can result from injury to peripancreatic vascular structures, leading to hemorrhage into the retroperitoneum. The peripancreatic inflammatory process can also cause thrombosis of major gastrointestinal vessels and result in ischemic lesions involving the stomach, small intestine, or colon that can cause bleeding. Management of these complications of pancreatitis is similar to that involved when they occur in the absence of pancreatitis.

Some patients with severe pancreatitism, develop DIC, but it rarely causes bleeding, and rarely needsprophylactic heparin.

Removal of precipitating factors, such as drugs or alcohol, is appropriate. Once the acute phase has been survived, by the end of the

first week, then local complications become pre-eminent in the management of these patients.

An indication for operative intervention in acute pancreatitis is the drainage of an infected pancreatic necrosis. These patients require removal of as much as possible of the infected necrosis and drainage for the remaining viable exocrine tissue. Current opinion is against debridement in sterile necrosis unless it is accompanied by life threatening systemic complications[17].

A pancreatic abscess usually occurs 2 to 6 weeks ,after an initial attack of acute pancreatitis, in contrast to infected necrosis ,which occurs in the first few hours or days. Treatment consists of external drainage, either by surgical or percutaneous catheter based measures[17].

Treatment of Biliary Pancreatitis

The presence of gallstones leading to choledocholithiasis is recognized as a major etiological factor worldwide. Endoscopic retrograde cholangio pancreatography (ERCP) has both diagnostic and most therapeutic utility in patients with biliary obstruction or cholangitis. By randomizing patients with AP to early ERCP versus no ERCP, both Neoptolemos and colleagues, and Fan and colleagues have

showed a significant decrease in morbidity but there was no significant improvement in mortality with routine use of ERCP. A metacentric randomized control study in the ERCP group by Folsch and colleagues recently, have demonstrated increased complication rate and mortality rate, after excluding the patients with biliary sepsis or obstruction. It therefore, found that early ERCP may be harmful even in the absence of ongoing biliary obstruction. Magnetic resonance cholangio pancreatography (MRCP) is an additional alternative to ERCP as a diagnostic tool that avoids the risk of post procedure pancreatitis.

In general, cholecystectomy as an early intervention, within the first 48 to 72 hours of admission, or delayed intervention (after 72 hours, but during the initial period of hospitalization) may be favored[8, 15]. Cholecystectomy with intra-operative CBD exploration is probably the best option for obstructive pancreatitis. However, high risk patients are best treated by endoscopic sphincterotomy, with clearance of stones by ERCP.

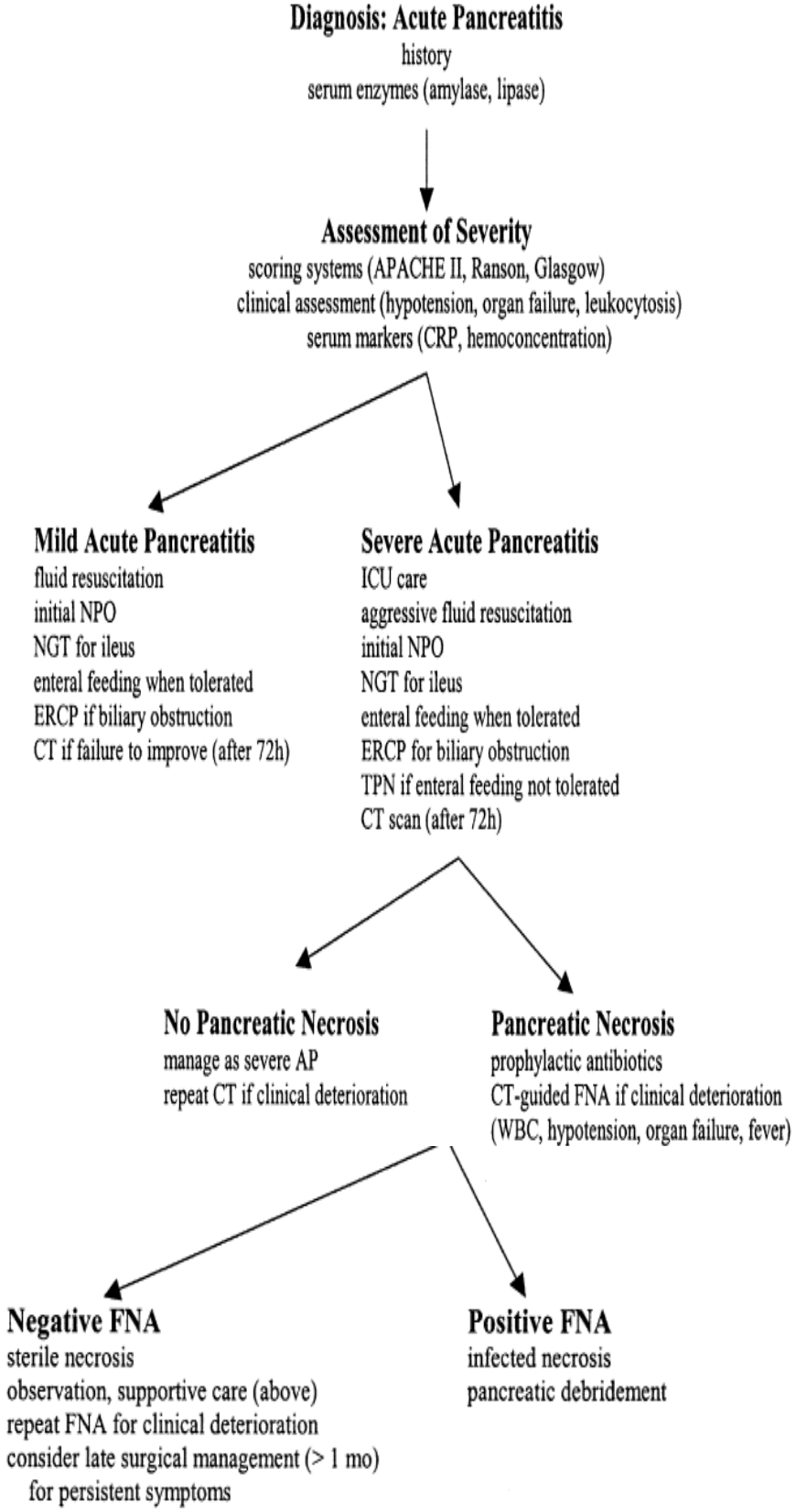
Surgical Management: Indications and Timing

Limited indications prevail for surgical intervention.Intervention is needed to address the etiology of pancreatitis or its complications. Suspected choledocholithiasis needs open or laparoscopic intervension.

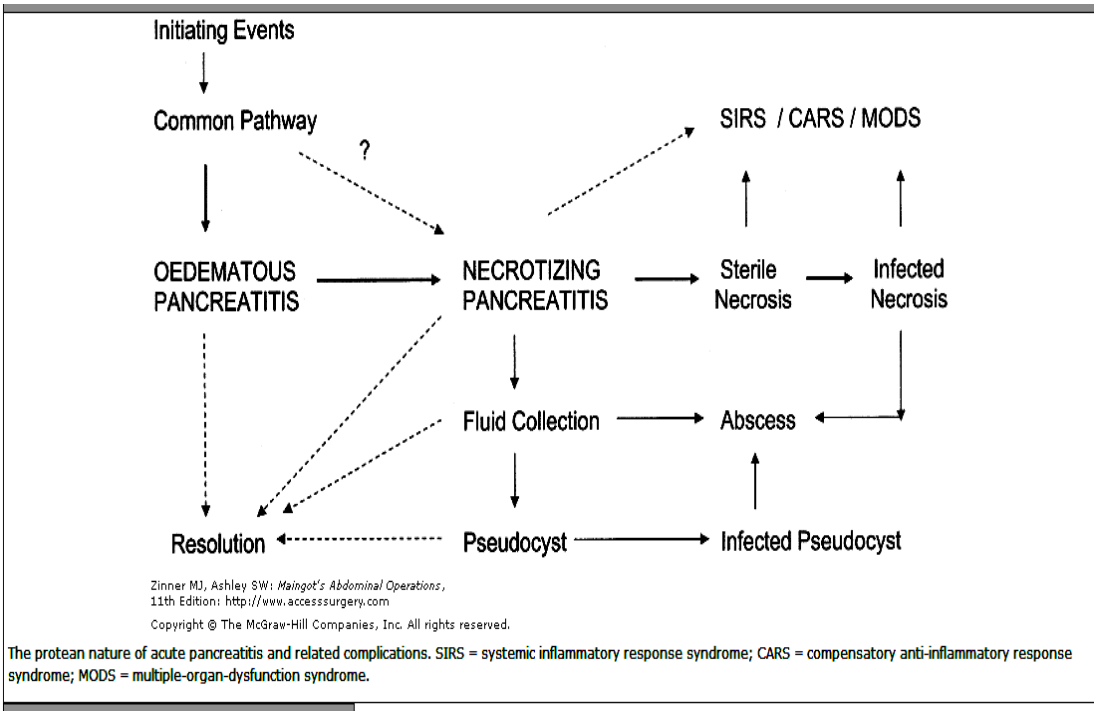
Delayed surgery is also, rarely needed for the treatment of local complications like pseudocysts[17].

Table 36–3. Indications for Surgical Intervention in Necrotizing Pancreatitis
Diagnostic uncertainty
Intra-abdominal catastrophe unrelated to necrotizing pancreatitis such as perforated viscus
Infected necrosis documented by FNA or extraluminal gas on CT
Severe sterile necrosis
Symptomatic organized pancreatic necrosis

Early surgical intervention leads to hemorrhage from the pancreatic bed, which may be difficult to control because the endarteritis obliterans was incomplete. Moreover the delineation between viable & non-viable tissue might not be clearly made out.


Diagnosis: Acute Pancreatitis
history
serum enzymes (amylase, lipase)
Assessment of Severity
scoring systems (APACHE II, Ranson, Glasgow)
clinical assessment (hypotension, organ failure, leukocytosis)
serum markers (CRP, hemoconcentration)
Mild Acute Pancreatitis
fluid resuscitation
initial NPO
NGT for ileus
enteral feeding when tolerated
ERCP if biliary obstruction
CT if failure to improve (after 72h)
Severe Acute Pancreatitis
ICU care
aggressive fluid resuscitation
initial NPO
NGT for ileus
enteral feeding when tolerated
ERCP for biliary obstruction
TPN if enteral feeding not tolerated
CT scan (after 72h)
No Pancreatic Necrosis
manage as severe AP
repeat CT if clinical deterioration
Pancreatic Necrosis
prophylactic antibiotics
CT-guided FNA if clinical deterioration
(WBC, hypotension, organ failure, fever)
Negative FNA
sterile necrosis
observation, supportive care (above)
repeat FNA for clinical deterioration
consider late surgical management (> 1 mo)
for persistent symptoms
Positive FNA
infected necrosis
pancreatic debridement

Complications[17]:



The protean nature of acute pancreatitis and related complications. SIRS = systemic inflammatory response syndrome; CARS = compensatory anti-inflammatory response syndrome; MODS = multiple-organ-dysfunction syndrome.

Complications may be classified as[15, 17]:

I. LOCAL:

Fluid collections

Pancreatic ascites/pleural effusion

Pancreatic pseudocyst

Pancreatic necrosis

Infected pancreatic abscess

Hemorrhage/pseudo aneurysm

II. REGIONAL:

Venous thrombosis

Paralytic ileus

Intestinal obstruction

Intestinal ischemia/necrosis

Cholestasis

III. SYSTEMIC:

A. Pulmonary

1. Pneumonitis, basal atelectasis
2. ARDS
3. Pleural effusion (L)

B. Cardiovascular

1. Hypotension
2. Hypovolemia
3. Sudden arrest &death
4. Nonspecific ECG(ST-T wave) changes
5. Pericardial effusion

C. Hematologic

1. Hemoconcentration
2. Disseminated intravascular coagulopathy

D. GI hemorrhage

1. Acid peptic disease
2. Gastric erosion
3. Portal/splenic vein thrombosis with variceal bleed

E. Renal

1. Oliguria
2. Azotemia
3. Renal vessel thrombosis

F. Metabolic

1. Hyperglycemic state
2. Hypocalcemic state
3. Hyperlipidemia (triglyceridemia)
4. Metabolic encephalopathy
5. Sudden loss of vision (Purtscher's retinopathy)

G. Central nervous system

1. Acute psychosis
2. Fat embolism occlusion
3. Alcohol withdrawal syndrome (AWS)

H. Fat necrosis

1. Intra-abdominal saponification
2. Subcutaneous tissue necrosis

SCORING SYSTEMS IN ACUTE PANCREATITIS

Pancreatitis is a serious disease with high morbidity and mortality rates. Some 80% were mild attack which recovers rapidly with conservative management. The rest of 20% were severe, with protracted course that needs intensive care and specialized management. Several predictors of severity are commonly used for this purpose[24].

Scoring systems can be used in predicting mortality, severity of disease and intensity of its complications. Prognostic factor analysis found to help in comparing the results, in-between the series of patients under study.

These systems include[25]:

- Ranson's criteria
- Balthazar computed tomography (CT) grading
- Imrie Glasgow coma score (GCS)
- Bank's clinical Criteria
- Simplified Acute Physiology Score(SAPS)
- Marshall Multiple organ failure (MOF) score and
- Acute physiology and chronic health evaluation (APACHE) I, II, III & O.

The GCS and Ranson's multiple scoring systems, require 48 hours of data collection; however, APACHE can be calculated at any time and shows prognostic correlation with acute pancreatitis, as increasing scores are associated with poor prognosis.

Once the acute pancreatitis has been diagnosed, assessment of severity is extremely important for execution of appropriate measures, preferably in an ICU setup with close monitoring.

AIMS AND OBJECTIVES OF THE STUDY

1. To know the usefulness of urine trypsinogen-2 in accurately diagnosing acute pancreatitis

2. To compare the diagnostic role of urine trypsinogen-2 with that of serum amylase, serum lipase and imaging studies in acute pancreatitis.

MATERIALS AND METHODS

Study design: Comparative Analytical study.

Setting: Department of General Surgery, Govt. Stanley Medical College and Hospital, Chennai. The study was conducted after obtaining the Institutional Ethical Committee approval (**annexure 2**).

Inclusion criteria:

1. Patients presenting with features suggestive of acute pancreatitis

2. Male and female subjects of age between 20 - 60 years shall be selected.

3. Adult subjects willing to give informed consent.

- **Exclusion criteria:**

1. Subjects below the age of 20 years and above the age of 60 years

2. Subject who are not willing to participate in the study

-

3. Individuals who are cognitively impaired and/or who are unable to give informed consent.

4. Proven cases of chronic pancreatitis and pancreatic cancer

5. Hereditary pancreatitis, cystic fibrosis

METHODOLOGY

- Patients presenting with acute upper abdominal symptoms like pain, vomiting, abdominal distention, admitted in the emergency department of our hospital from January 2013 to November 2013 are enrolled in the study.

- Urine sample were obtained from all the patients and tested with Spot Urine trypsinogen-2 dipstick.

- Serum amylase and serum lipase tests were also simultaneously done in these patients.

- Patients are also evaluated with (USG) abdomen and (CECT) abdomen,if required.

- Final diagnosis of acute pancreatitis is made on the basis of clinical picture, serum amylase more than threefold rise and radiological findings.

- Urine trypsinogen-2 dipstick test were compared with serum amylase, serum lipase and imaging studies in patients with final diagnosis of acute pancreatitis

- Observations are tabulated according to the pre-designed proforma.

- The results are analyzed using Microsoft Excel for tabular transformation and graphical representation. For comparing the parameters, Chi Square test or Fischer's exact test are used. SPSS software will be used for statistical analysis.

OBSERVATION &RESULTS

This study was conducted in the Department of General Surgery, Govt. Stanley Medical College & Hospital, Chennai for a period of one year. The 100 persons ,who fulfilled the inclusion criteria ,were enrolled in this study, after obtaining an informed consent.

Table: 1 AGE DISTRIBUTION

Age Range (years)	No. of patients	Percentage (%)
21yrs - 30yrs	24	**24**
31yrs - 40yrs	25	**25**
41yrs - 50yrs	36	**36**
51yrs - 60yrs	13	**13**
>60yrs	2	**2**
Total	**100**	**100 %**

The age group of patients enrolled in this study ranges from 20 to 80 yrs. The peak incidence was noted in the 4^{th} decade of life.

Figure : 1 AGE DISTRIBUTION

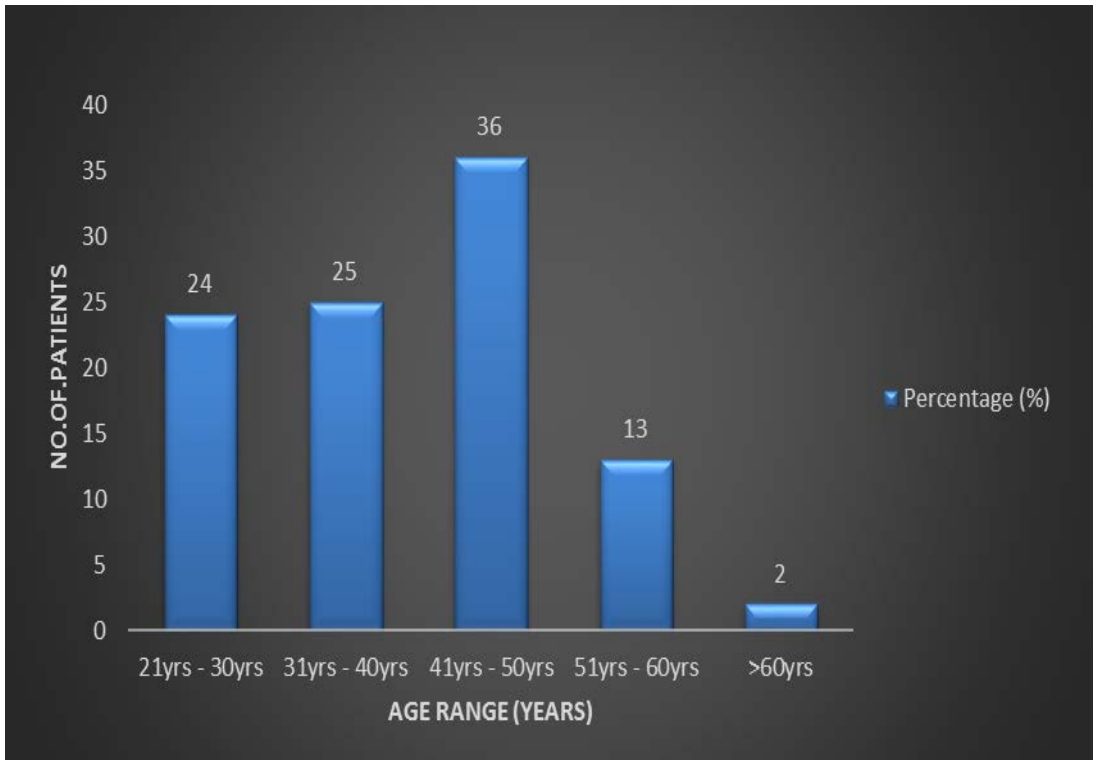


Table: 2 GENDER DISTRIBUTIONS

Sex	No. of patients	Percentage (%)
Male	84	84
Female	16	16
Total	100	100

Out of 100 patients enrolled in this study, there were 84 male and 16 female patients.

Male: Female ratio-5.25:1

Figure:2 GENDER DISTRIBUTION

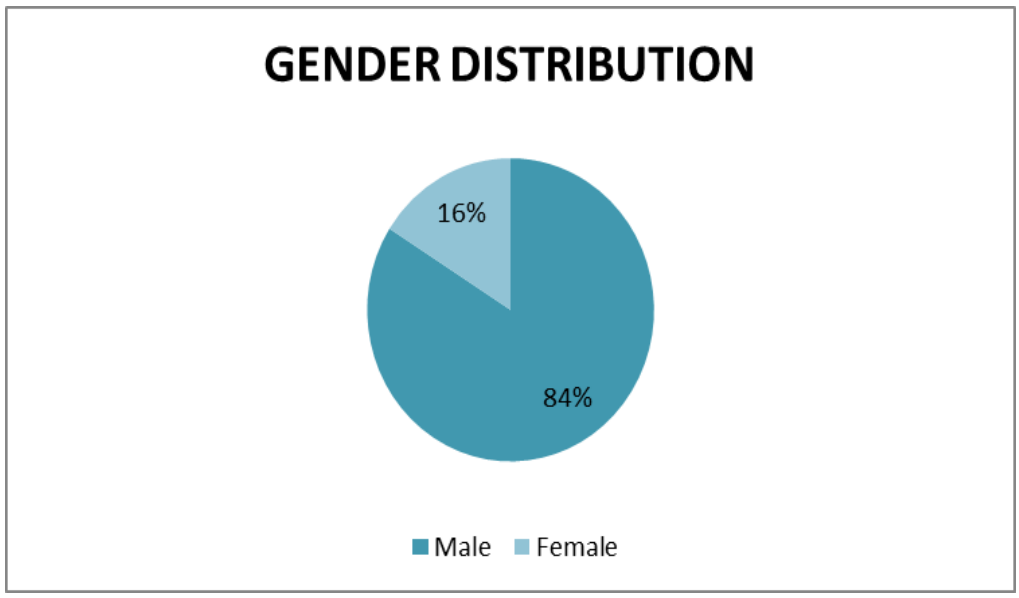


Table:3 GENDER DISTRIBUTION IN ACUTE PANCREATITIS

Gender	Acute pancreatitis(61)	Percentage(%)
MALE	57	93.44
FEMALE	4	6.55

Of the total cases of Acute Pancreatitis,93% of patients were male and the rest were female.

Figure:3 GENDER DISTRIBUTION IN ACUTE PANCREATITIS(n=61)

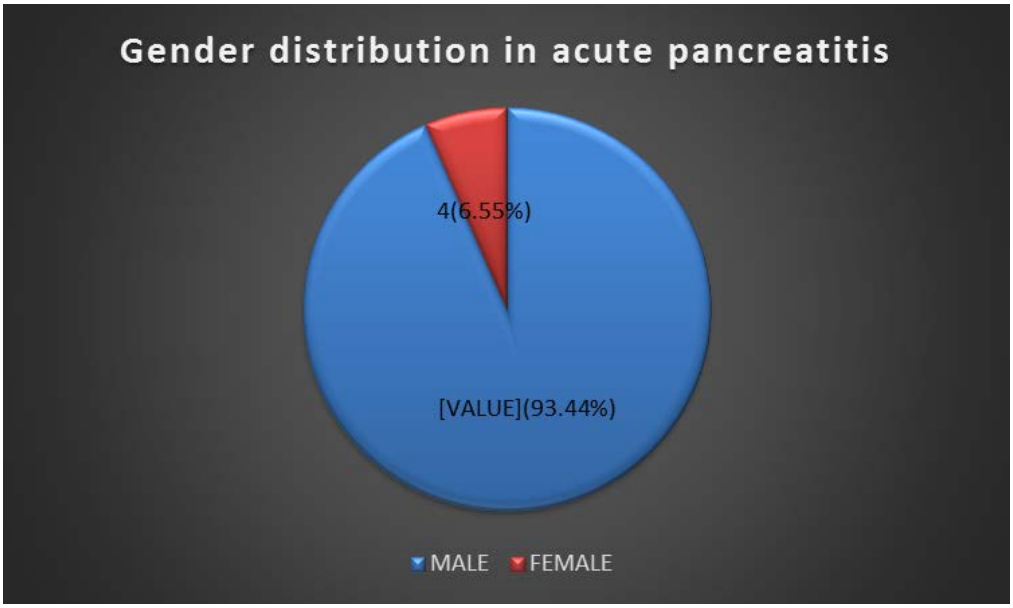


Table: 4 CLINICAL FEATURES:

Symptoms	No. of patients	Percentage (%)
Pain abdomen	61	61
Fever	25	25
Vomiting	54	54
Jaundice	12	12
Abdominal distension	32	32

On clinical presentation,61% of patients presented with abdominal pain as chief complain. Rest of the patients had vomiting, abdomen distension and fever along with the presenting symptoms.

Figure:4 CLINICAL FEATURES

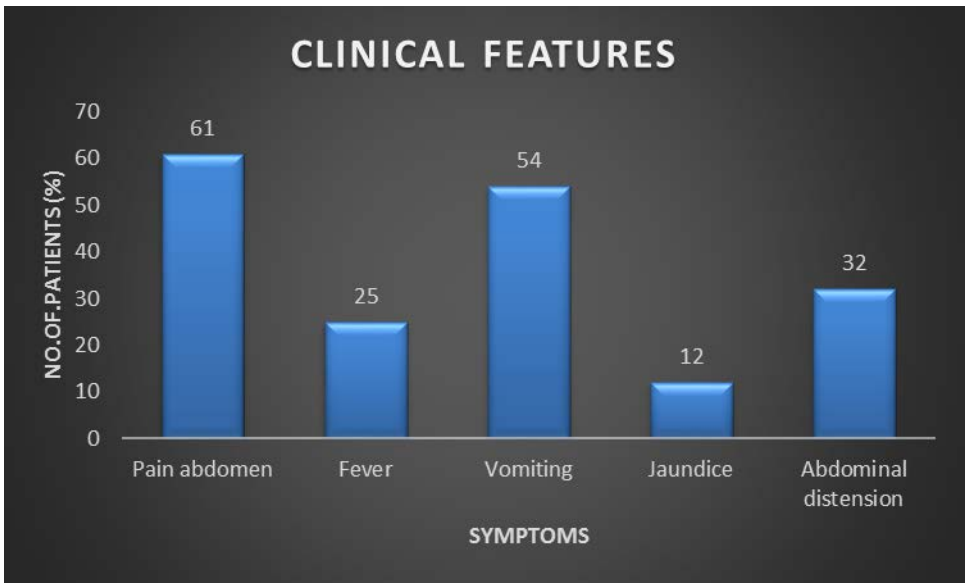


Table: 5 ETIOLOGY

Etiology	No. of patients	Percentage (%)
Alcohol	53	86.89
Gall stone disease	5	8.19
Post ERCP	1	1.64
Hypertriglyceridemia	2	3.28
Total	61	100

History of consumption of alcohol and the possibility of it being the etiological factor were found in 53 patients. Gall stone disease was attributed in 5 patients. Hyperlipidemia and Post ERCP, as a causative factor in 2 & 1 patients, respectively.

Figure: 5 ETIOLOGY

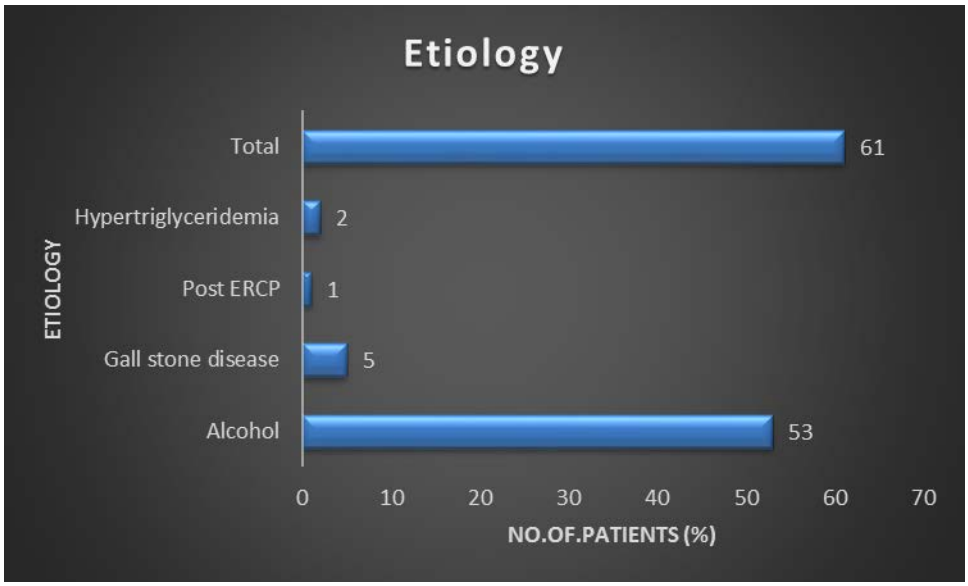


Table:6 COMPARISON OF DIFFERENT PARAMETERS USED IN THE DIAGNOSIS OF ACUTE PANCREATITIS

Parameters	Acute Pancreatitis(61)	Others(39)	Total(100)
AMYLASE	45	4	49
LIPASE	36	4	40
USG	53	-	53
CECT	14	-	14
TRYPSINOGEN	48	3	51

Table:7 COMPARISON OF SENSITIVITY AND SPECIFICITY OF DIFFERENT PARAMETERS

Parameters	Sensitivity	Specificity
AMYLASE	73.77	89.74
LIPASE	59.02	89.74
TRYPSINOGEN	78.69	92.31

Table 8: ESTIMATION OF SIGNIFICANCE OF THE TEST

Urine trypsinogen	Acute Pancreatitis	Non pancreatic causes	Total
Positive	48	3	51
Negative	13	36	49
TOTAL	61	39	100

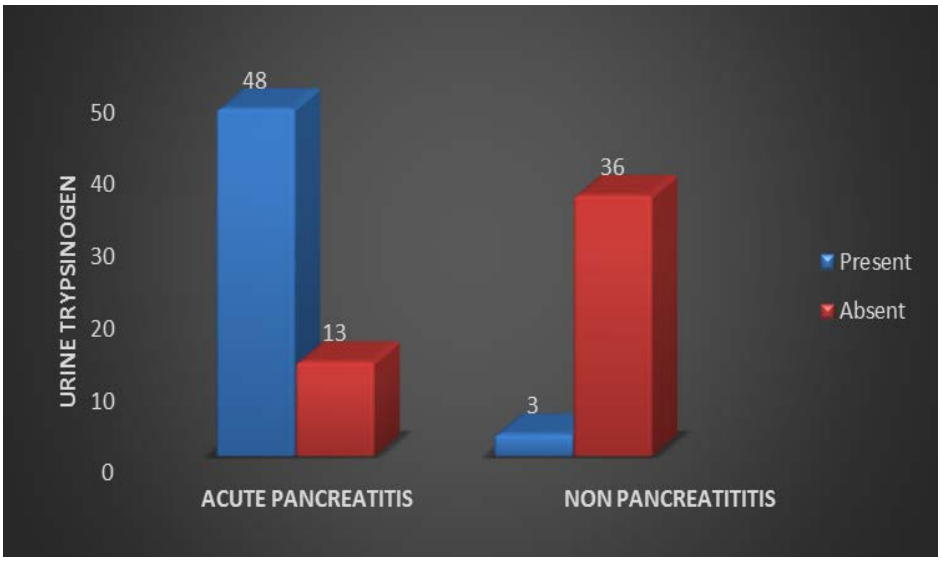
Sensitivity= a/(a+c) ;48/61=78.6%

Specificity=d/(b+d);36/39=92.3%

Using Kappa statistics the value was found to be 0.67

(Based on criteria originally proposed by Landis and Koch: kappa values greater than about 0.75 are often taken as representing excellent agreement; those between 0.4 and 0.75 as fair to good agreement; and those less than 0.4 as moderate or poor agreement.)

FIGURE 6: ANALYSIS OF TRYPSINOGEN TEST



DISCUSSION

Trypsinogen, a precursor of trypsin is required for protein digestion. Premature trypsin activation leads to pancreatic self-digestion. Trypsinogen is a 25-kd pancreatic proteinase. In human pancreatic juice, there are three trypsinogen (TPS) isoenzymes, namely, cationic (TPS-1) and anionic TPS (TPS-2), and a minor isoenzyme (TPS-3).

The inactive form of trypsinogen,stored in the cytoplasmic zymogen granules of pancreatic acinar cells, are secreted into the adjacent duct lumen and are subsequently delivered to the small intestine.Within the intestine, they are activated by enterokinase. Premature activation of trypsinogen to trypsin within the pancreas,is the prime pathophysiologic event, in the development of acute pancreatitis. Under normal conditions, trypsinogen are secreted into pancreatic fluid, and only a small amount enters the circulation. For unknown reason, the tubular reabsorption of trypsinogen-2 is lower than trypsinogen-1.

The urinary trypsinogen-2 dipstick test is proposed to be, a rapid and simple method for the early diagnosis of acute pancreatitis. Urine trypsinogen-2 concentrations were measured using a dipstick test

(Actim Pancreatitis, Medix Biochemica Oy AB,Kauniainen, Finland) based on an immunochromatography assay. The detection limit of the test is approximately 50 ng/mL. The test strip has a control line and two lines indicate a positive result. The test results can be read after 5 minutes.

The test strip, dipped into the urine sample, contains trypsinogen-2 bound to monoclonal antibody labelled blue latex particles, which migrate across a nitrocellulose membrane with a zone containing another antibody specific for epitope on trypsinogen-2.

Two retrospective studies[10, 27] carried out by a Finnish group showed that Urine Trypsinogen-2 had better sensitivity and specificity in predicting Acute Pancreatitis than amylase and lipase. A later larger prospective cohort study[28] by the same group enrolling 53 patients with AP and 447 patients with AAD (non-pancreatic) showed that Urine Trypsinogen-2 has a sensitivity of 94% and a specificity of 95%, better than serum amylase (85% and 91%) and urinary amylase (83% and 88%) in predicting Acute Pancreatitis.

Sensitivity of amylase and lipase was found to be 73.77% and 59.02% respectively, whereas as sensitivity of trypsinogen was found to be 78.69%. Specificity of amylase and lipase was found to be 89.74%

and 89.74% respectively, whereas as specificity of trypsinogen was found to be 92.1%.Analysing the data,it is found that sensitivity and specificity of trypsinogen is higher than the routine investigations. Eventhough it has a low range of sensitivity, its high specificity ensures that the test can be used as a screening test to check the true negative cases.

False positive results is seen in 3 of the 39 non-pancreatitis cases, namely two cases of Gallstones and one case of renal failure. In case of renal failure, defect in the excretion of trypsinogen makes the result positive. In case of gallestone, studies with more sample size has to be conducted to analyse the etiology of the positivity of the test.

CONCLUSION AND SUMMARY

1. Urine Trypsinogen-2 dip stick test is a simple, rapid, easy, and noninvasive test which can diagnose or rule out, most of the cases of acute pancreatitis.

2. Urine Trypsinogen-2 estimation doesn't require laboratory facilities. It is undertaken almost instantaneously (within 5 minutes) as opposed to serum amylase and lipase, results for which may require an hour to get back to the physician.

3. The urinary trypsinogen-2 test could be used as a screening test for acute pancreatitis.

4. Modification of the cutoff point of this assay increases the specificity to the point where it can be used for diagnosis.

5. Qualitative rapid urine trypsinogen-2 test strip is easy to perform. And hence it has been shown to be a reliable and useful screening test for acute pancreatitis in daily practice [12-16], particularly in healthcare units lacking laboratory facilities.

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PROFORMA

SL. NO:

- **NAME :**
- **AGE /SEX:**
- **IP NO:**
- **ADDRESS WITH CONTACT NUMBER:**

- **DATE OF ADMISSION:**
- **DATE OF SURGERY:**
- **DATE OF DISCHARGE:**

HISTORY OF PRESENTING ILLNESS:

H/O abdomen pain

Duration

Nature of pain

onset

Progression

Radiating

Aggravating/relieving factors

H/O vomiting

Nature of vomitus

No. of episodes

Associated with hemetemesis

H/O Fever

Duration

Nature

Associated with chills & rigor:

H/O jaundice

H/O abdomen distension

H/O loss of appetite

H/O loss of weight

PAST HISTORY:

DM/hypertension/asthma/TB/epilepsy/cardiac illness

H/o similar episodes in the past, if any:

H/o major illness/ hospital admissions, if any

PERSONAL HISTORY:

Occupation

Socio-economic status

Alcohol

Smoking

Drug addiction

FAMILY HISTORY:

TREATMENT HISTORY:

CLINICAL EXAMINATION:

General examination: Pallor Icterus

Pulse

BP

Temperature

Respiratory Rate

Systemic examination:

CVS

RS

CNS

Abdomen

CLINICAL DIAGNOSIS:

INVESTIGATIONS:

CBC:Hemoglobin

TC/DC:

ESR

PLATELET

RFT:BLOOD UREA

SERUM CREATINE

SODIUM

POTASSIUM

RANDOM BLOOD SUGAR

CHLORIDE

LFT:TOTAL BILIRUBIN

DIRECT BILIRUBIN

INDIRECT BILIRUBIN

SGOT /SGPT

ALKALINE PHOSPATASE

TOTAL PROTEIN

ALBUMIN

X-RAY ABDOMEN

X-RAY CHEST

URINE TRYPSINOGEN-2 DIPSTICK:

SERUM AMYLASE

SERUM LIPASE

USG ABDOMEN

CECT ABDOMEN

FINAL DIAGNOSIS:

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A study on role of urine trypsinogen-2 in Diagnosing Acute Pancreatitis

Principal Investigator : Dr.N.Sangara Narayanan

Designation : PG in MS (General Surgery)

Department : Department of General Surgery
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 08.04.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

13/9/13

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MASTER CHART

sl_no	name	ip_no	age	sex	abd_ pain	fever	vomiting	jaundice	abd_ distension	alcohol	gall_stone	post_ercp	hyper_tg	amylase	lipase	usg	ct	urine_ trypsinogen	diagnosis
1	Jegan	38392	45	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
2	Anandhan	37332	42	Male	1	1	1	1	1	1	2	2	2	1	1	1	99	1	1
3	Dhanapal	34612	55	Male	1	1	1	2	1	1	2	2	2	1	1	1	99	1	1
4	Murugan	37377	40	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
5	Premkumar	26628	29	Male	1	1	1	1	1	1	2	2	2	2	2	2	1	2	1
6	Chellakannu	26301	34	Male	1	1	1	2	1	2	1	2	2	2	2	1	1	1	1
7	Rajendran	46982	46	Male	1	1	1	2	1	1	2	2	2	1	1	3	3	2	5
8	Rafiq	18441	50	Male	1	1	1	2	1	1	2	2	2	2	2	2	1	2	1
9	Prakash	23987	29	Male	1	1	1	1	1	1	2	2	2	2	2	2	1	2	1
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12	Arunprasath	39206	32	Male	1	1	1	2	1	2	1	2	2	1	1	1	1	1	1
13	Gopinath	22530	31	Male	1	2	1	2	1	1	2	2	2	1	1	1	99	1	1
14	Prabu	22444	31	Male	1	2	2	2	2	1	2	2	2	2	2	1	99	2	1
15	Senthil pandi	6923	32	Male	1	1	1	2	2	1	2	2	2	2	2	4	99	2	2
16	Prabu	17439	21	Male	1	1	1	2	2	1	2	2	2	2	2	2	1	2	1
17	Arivazhagan	19405	46	Male	1	1	1	1	1	1	2	2	2	1	1	1	99	1	1
18	Kannan	26665	32	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
19	Pillayarsamy	37807	49	Male	1	2	2	2	2	1	2	2	2	2	2	1	99	2	1
20	Vijayakumar	36395	35	Male	1	2	1	2	2	2	2	2	2	2	2	99	99	2	3
21	Krishnan	37386	55	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
22	Murugan	39214	35	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
23	Rajam	39206	56	Male	1	1	1	2	2	1	2	2	2	1	1	4	3	2	7
24	Pushpavalli	39216	45	Female	1	1	1	2	1	2	2	2	2	2	2	3	3	1	5
25	Mariselvam	42570	24	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
26	Mohan	37469	50	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
27	Aruna	37419	30	Female	1	1	1	2	2	2	2	2	2	2	2	4	99	2	2
28	Munusamy	49947	42	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
29	Prakash	50684	25	Male	1	1	1	1	1	1	2	2	2	2	2	2	1	2	1
30	Aruldas	38435	60	Male	1	1	1	2	1	1	2	2	2	1	1	1	99	1	1
31	Malleswari	42262	24	Female	1	1	1	2	2	2	2	2	2	2	2	3	99	2	2
32	Wilson	40677	39	Male	1	2	1	2	2	1	2	2	2	2	2	99	99	2	3

33	Srinivasan	42845	30	Male	1	1	1	2	2	1	2	2	2	2	2	4	99	2	2
34	Ramesh	42942	38	Male	1	2	1	2	2	1	2	2	2	2	2	99	99	2	3
35	Syed ibrahim	42947	32	Male	1	1	1	2	2	2	2	2	2	2	2	4	99	2	2
36	Vijayakumar	34459	40	Male	1	2	1	2	2	1	2	2	2	2	2	99	99	2	3
37	Elumalai	34520	47	Male	1	2	1	2	1	1	2	2	2	1	1	1	99	1	1
38	Manimegalai	34781	49	Female	1	1	1	1	2	2	1	2	2	2	2	3	3	2	6
39	Kathiresan	33291	42	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
40	Raju	33413	40	Male	1	2	1	2	2	1	2	2	2	2	2	99	99	2	3
41	Pattamal	30611	53	Female	1	2	1	2	1	1	2	2	2	1	1	1	99	1	1
42	Jayaraman	33444	27	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
43	Nagarajan	32075	57	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
44	Palani	32520	32	Male	1	2	2	2	2	1	2	2	2	2	2	1	99	2	1
45	Baskar	28928	48	Male	1	1	1	2	1	1	2	2	2	1	1	1	99	1	1
46	Gayathri	30619	22	Female	1	1	1	2	2	2	2	2	2	2	2	3	99	2	2
47	Nagaboosanam	28937	38	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
48	Ayyappan	29188	27	Male	1	1	1	2	1	1	2	2	2	1	1	1	99	1	1
49	Sivasankari	29136	34	Female	1	2	1	2	2	2	2	2	2	2	2	99	99	2	3
50	Premkumar	26628	29	Male	1	1	1	1	1	1	2	2	2	2	2	2	1	2	1
51	Vincent	26849	28	Male	1	1	1	2	2	2	2	2	2	2	2	3	99	2	2
52	Sivaranjani	26682	60	Female	1	1	2	1	1	2	2	2	2	2	2	3	3	2	8
53	Kumar	25379	46	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
54	Babu	25328	30	Male	1	1	1	2	1	2	2	2	1	1	1	1	99	1	1
55	Santhi	24611	32	Female	1	1	1	2	1	2	2	2	2	1	1	4	3	1	7
56	Ramamoorthy	24700	48	Male	1	1	1	1	1	1	2	2	2	2	2	3	3	2	5
57	Selvakumar	22840	30	Male	1	1	1	2	2	1	2	2	2	2	2	3	99	2	2
58	Subramani	22619	56	Male	1	1	2	2	1	1	2	2	2	2	2	3	3	2	8
59	Govindhammal	40173	27	Female	1	1	1	2	2	2	2	2	2	2	2	3	99	2	2
60	Rajendran	22757	50	Male	1	1	2	1	1	1	2	2	2	1	1	3	3	2	6
61	anandhi	21681	38	Female	1	1	1	1	1	2	1	2	2	2	2	1	1	1	1
62	Ramalingam	21240	45	Male	1	1	1	2	2	1	2	2	2	2	2	99	99	2	4
63	Jayakumar	49951	80	Male	1	2	1	2	1	1	2	2	2	1	1	1	99	1	1
64	Vasudevan	7827	48	Male	1	1	1	1	2	2	1	2	2	2	2	3	3	2	6
65	Munusamy	34601	60	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
66	Shanmugam	35947	47	Male	1	1	1	2	1	1	2	2	2	2	2	3	3	2	5
67	Udayakumar	34982	34	Male	1	2	1	2	2	2	2	2	2	2	2	99	99	2	3
68	Eswari	17445	37	Female	1	2	1	2	2	2	2	2	2	2	2	99	99	2	3
69	Kumar	17447	24	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1

70	Suganthi	28542	27	Female	1	1	1	2	1	2	2	2	1	2	2	2	1	1	1
71	Nandha	433112	55	Male	1	2	2	2	2	1	2	2	2	1	1	1	99	1	1
72	Vasanth	45186	23	Male	1	1	1	2	2	2	2	2	2	2	2	3	99	2	2
73	Veeraiah	38112	42	Male	1	1	1	2	2	2	2	2	2	2	2	99	99	2	4
74	Loganathan	43336	50	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
75	Amsa	2461	52	Female	1	1	1	1	1	2	1	2	2	2	2	1	1	1	1
76	Ragaramya	3382	36	Female	1	2	1	2	2	2	2	2	2	2	2	99	99	2	3
77	Sengootuvan	33501	45	Male	1	1	2	2	2	1	2	2	2	2	2	99	99	2	4
78	Krishnamoorthy	51474	45	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
79	Anandhan	26918	47	Male	1	1	1	1	1	2	1	2	2	1	1	1	1	1	1
80	Pillaiyarsamy	37807	49	Male	1	2	2	2	2	1	2	2	2	2	2	1	99	2	1
81	Arivazhagan	32076	46	Male	1	1	1	1	1	1	2	2	2	1	1	1	99	1	1
82	Suresh	24123	24	Male	1	1	1	2	2	2	2	2	2	2	2	3	99	2	2
83	Nageswara rao	64734	25	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
84	Arun	31829	45	Male	1	1	1	2	1	2	2	1	2	1	1	1	1	1	1
85	Bagiyanathan	28043	26	Male	1	1	1	2	1	1	2	2	2	1	1	1	99	1	1
86	Abdulhameed	28086	72	Male	1	1	1	1	1	1	2	2	2	1	1	1	99	1	1
87	Gani	29630	45	Male	1	2	1	2	1	1	2	2	2	1	1	1	99	1	1
88	Sivaraman	30475	50	Male	1	1	1	2	2	1	2	2	2	2	2	4	3	1	7
89	Naseer hussain	29624	45	Male	1	2	2	2	2	1	2	2	2	1	1	1	99	2	1
90	Rajendran	34711	45	Male	1	1	1	2	2	2	2	2	2	2	2	99	99	2	4
91	Rangaraj	35579	40	Male	1	2	1	2	2	1	2	2	2	2	2	99	99	2	3
92	Murugammal	36497	30	Female	1	1	1	2	2	2	2	2	2	2	2	4	99	2	2
93	Palani	36509	37	Male	1	2	2	2	2	1	2	2	2	2	2	1	99	2	1
94	Dilly	35639	60	Male	1	2	1	2	1	1	2	2	2	1	1	1	99	1	1
95	Mabu basha	35685	45	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
96	Ekambaram	38263	50	Male	1	2	1	2	1	1	2	2	2	1	1	1	99	1	1
97	Kamaleswaran	51612	32	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1
98	Radhakrishnan	51658	55	Male	1	1	1	2	1	1	2	2	2	2	2	2	1	2	1
99	Rajesh	33762	45	Male	1	1	1	2	2	2	2	2	2	2	2	99	99	2	4
100	Jeeva	34448	41	Male	1	2	1	2	2	1	2	2	2	1	1	1	99	1	1

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